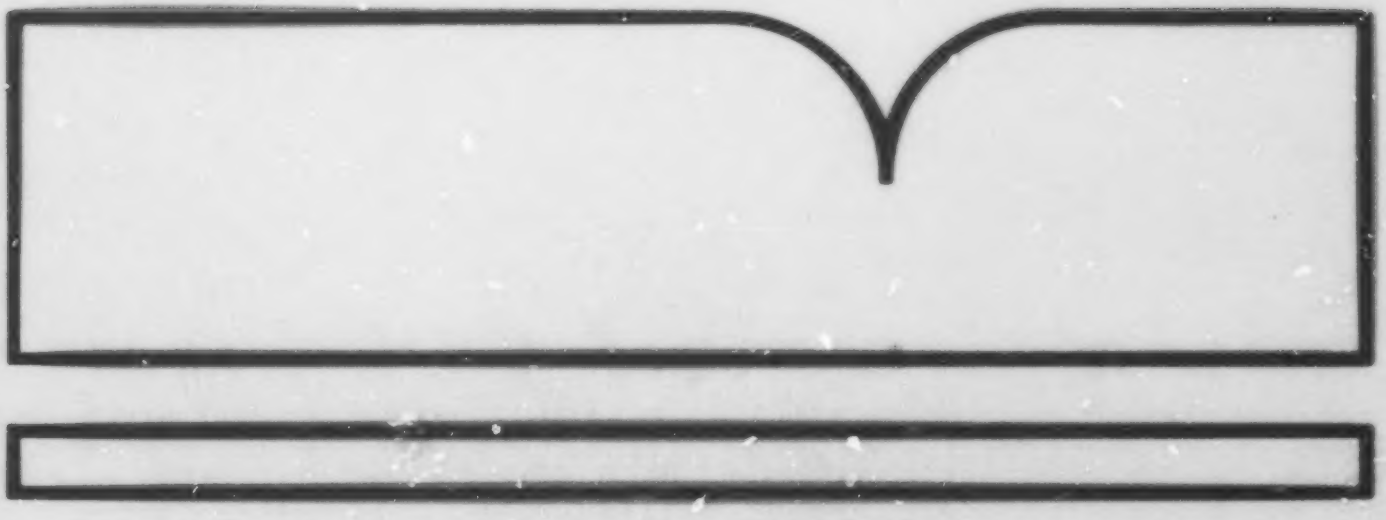
PB88-180534

# Health and Environmental Effects Profile for Methyl Parathion

(U.S.) Environmental Protection Agency
Cincinnati, OH

Sep 84



U.S. Department of Commerce
National Technical Information Service
NTIS

**TECHNICAL REPORT DATA**
*(Please read Instructions on the reverse before completing)*

| | |
|---|---|
| 1. REPORT NO. EPA/600/X-84/329 | 2. |
| 3. RECIPIENT'S ACCESSION NO. PB88 180534/AS | |
| 4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Methyl Parathion | 5. REPORT DATE |
| | 6. PERFORMING ORGANIZATION CODE |
| 7. AUTHOR(S) | 8. PERFORMING ORGANIZATION REPORT NO. |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS | 10. PROGRAM ELEMENT NO. |
| | 11. CONTRACT/GRANT NO. |
| 12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268 | 13. TYPE OF REPORT AND PERIOD COVERED |
| | 14. SPONSORING AGENCY CODE EPA/600/22 |

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Health and Environmental Effects Profile for methyl parathion was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Methyl parathion has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for methyl parathion is 0.28 mg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a relase as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

17. KEY WORDS AND DOCUMENT ANALYSIS

| a. DESCRIPTORS | b. IDENTIFIERS/OPEN ENDED TERMS | c. COSATI Field/Group |
|---|---|---|
| | | |

| | | |
|---|---|---|
| 18. DISTRIBUTION STATEMENT Public | 19. SECURITY CLASS (This Report) Unclassified | 21. NO. OF PAGES 89 |
| | 20. SECURITY CLASS (This page) Unclassified | 22. PRICE PC A04/MF A01 6.95 |

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB88-180534

EPA/600/X-84/329
September 1984

# HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR METHYL PARATHION

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

## DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

## PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of $q_1^*$ (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

TABLE OF CONTENTS


| | | Page |
|---|---|---|
| 1. | INTRODUCTION | 1 |
| 1.1. | STRUCTURE AND CAS NUMBER | 1 |
| 1.2. | PHYSICAL AND CHEMICAL PROPERTIES | 1 |
| 1.3. | PRODUCTION DATA | 2 |
| 1.4. | USE DATA | 2 |
| 2. | ENVIRONMENTAL FATE AND TRANSPORT | 3 |
| 2.1. | AQUATIC | 3 |
| 2.2. | SOILS | 5 |
| 2.3. | AIR | 8 |
| 3. | EXPOSURE | 9 |
| 4. | PHARMACOKINETICS | 12 |
| 4.1. | ABSORPTION | 12 |
| 4.2. | DISTRIBUTION | 13 |
| 4.3. | METABOLISM | 15 |
| 4.4. | EXCRETION | 16 |
| 5. | EFFECTS | 18 |
| 5.1. | CARCINOGENICITY | 18 |
| 5.2. | MUTAGENICITY | 19 |
| 5.3. | TERATOGENICITY | 24 |
| 5.4. | OTHER REPRODUCTIVE EFFECTS | 27 |
| 5.5. | CHRONIC AND SUBCHRONIC TOXICITY | 27 |
| 5.6. | OTHER RELEVANT INFORMATION | 33 |
| 6. | AQUATIC TOXICITY | 39 |
| 6.1. | ACUTE EFFECTS | 39 |
| 5.2. | CHRONIC EFFECTS | 46 |
| 6.3. | PLANT EFFECTS | 47 |
| 6.4. | RESIDUES | 48 |
| 6.5. | OTHER RELEVANT INFORMATION | 48 |
| 7. | EXISTING GUIDELINES AND STANDARDS | 50 |
| 7.1. | HUMAN | 50 |
| 7.2. | AQUATIC | 51 |
| 8. | RISK ASSESSMENT | 52 |
| 9. | REFERENCES | 56 |
| APPENDIX: | LITERATURE SEARCHED | 80 |

## LIST OF TABLES


| No. | Title | Page |
|---|---|---|
| 3-1 | Monitoring Data for Methyl Parathion. . . . . | 11 |
| 4-1 | Distribution of $^{32}P$ in the Tissues of Rats and Guinea Pigs, 2.5 Minutes After Intravenous Ingestion of $^{32}P$-Methyl Parathion . . . . . | 14 |
| 5-1 | Mutagenicity Testing of Methyl Parathion in Prokaryotic Systems . . . . . | 20 |
| 5-2 | Mutagenicity Testing of Methyl Parathion in Eukaryotic Systems. . . . . | 21 |
| 5-3 | Values for Acute $LD_{50}$ and $LC_{50}$ of Methyl Parathion. . . . . | 34 |
| 6-1 | Acute Lethal Effects of Methyl Parathion to Freshwater Fish . . . . . | 40 |
| 6-2 | Acute Lethal Effects of Methyl Parathion to Marine Organisms. . . . . | 44 |

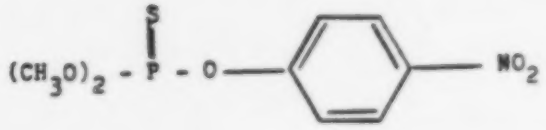
## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADI | Acceptable daily intake |
| BCF | Bioconcentration factor |
| bw | Body weight |
| CNS | Central nervous system |
| DNA | Deoxyribonucleic acid |
| $EC_{50}$ | Median Effective Concentration |
| GI | Gastrointestinal |
| i.p. | Intraperitoneal |
| i.v. | Intravenous |
| $LC_{50}$ | Concentration lethal to 50% of recipients (and all other subscripted dosage levels) |
| $LD_{50}$ | Dose lethal to 50% of recipients (and all other subscripted dosage levels) |
| LOEL | Lowest-observed-effect level |
| MATC | Maximum acceptable toxicant concentration |
| MSS | Maximum sustained swimming speed |
| MTD | Maximum tolerable dose |
| NOEL | No-observed-effect level |
| ppb | Parts per billion |
| ppm | Parts per million |
| RBC | Red blood cell |
| s.c. | Subcutaneous |
| TLV | Threshold limit value |
| TWA | Time-weighted average |

# 1. INTRODUCTION

## 1.1. STRUCTURE AND CAS NUMBER

Methyl parathion is the common name for O,O-dimethyl O-p-nitrophenyl phosphorothionate. This chemical has several synonyms, including parathion-methyl; phosphorothioic acid, O-O-dimethyl-O-(4-nitrophenyl)ester; O,O-dimethyl-O-4-nitrophenyl phosphorothionate. It is marketed under the trade names Dalf, Folidol-M, Nitrox-80, Bladan M, and a variety of other names (Worthing and Walker, 1983; IARC, 1983). The structure of methyl parathion is given below:



Molecular formula: $C_8H_{10}NO_5PS$

Molecular weight: 263.2

The Chemical Abstract Services (CAS) Registry number for this compound is 298-00-0.

## 1.2. PHYSICAL AND CHEMICAL PROPERTIES

Methyl parathion is a white crystalline solid, but the technical product is a light to dark tan liquid of ~80% purity (Worthing and Walker, 1983). Some of the physical properties of methyl parathion are given below (Worthing and Walker, 1983 unless otherwise stated.)

| | |
|---|---|
| Melting point: | 35-36°C |
| Density $d_4^{20}$: | 1.358 |
| Solubility in water at 25°C: | 55-60 mg/ℓ |
| Vapor pressure at 20°C: | $9.7 \times 10^{-6}$ mm Hg |

| | |
|---|---|
| Log octanol/water partition coefficient: | 2.86 (Hansch and Leo, 1981) |
| Soil sorption coefficient ($K_{OC}$): | $3.5 \times 10^3$ to $7.7 \times 10^4$ (Davidson et al., 1980; Smith et al., 1978; Reinbold et al., 1979). |

The compound is hydrolyzed rapidly by alkalis, and isomerizes readily to the O,S-dimethyl analog upon heating (Worthing and Walker, 1983).

## 1.3. PRODUCTION DATA

Methyl parathion is commercially produced by the reaction of O,O-dimethyl phosphorochloridothionate obtained through phosphorus pentasulfide ($P_2S_5$), methanol and chlorine, and the sodium salt of 4-nitrophenol in acetone solvent (Von Rumker et al., 1974). In the 1970s, a number of companies produced methyl parathion in the United States (Von Rumker et al., 1974). According to USITC (1983) and SRI (1983), Monsanto Co. Anniston, AL, was the only producer of this chemical in 1982 and 1983. No estimate of the present annual United States production data for this chemical is available, but the combined annual production capacity for parathion and methyl parathion may be ~29 million kg (IARC, 1983).

## 1.4. USAGE DATA

Methyl parathion is a broad-spectrum, nonsystemic contact and stomach insecticide used to control insects on a wide variety of crops (Worthing and Walker, 1983; IARC, 1983). Some of the crops for which methyl parathion is used are cotton, soybean, alfalfa, some vegetable crops, deciduous fruits and nuts, and tobacco (IARC, 1983). The largest volume (~85% in 1978) of methyl parathion in the United States was used on cotton (IARC, 1983).

## 2. ENVIRONMENTAL FATE AND TRANSPORT

### 2.1. AQUATIC

The fate of methyl parathion in aquatic media under various laboratory and field conditions has been studied by a number of investigators. The biodegradation of methyl parathion by aufwuchs (microbial growth attached to submerged surfaces or suspended in streamers or mats) microorganisms in aquatic media was studied by Lewis and Holm (1981). The second-order biodegradation rate constant was determined to be $4.5 \times 10^{-11}$ $\ell$ cell$^{-1}$ hr$^{-1}$. If one assumes the concentration of microorganisms in river water to be $10^6$ cell $\ell^{-1}$ (Burns et al., 1982), the half-life of this compound due to biodegradation in river water can be estimated to be ~6 days. The concentration of microorganisms capable of degrading methyl parathion is dependent upon the nature of the body of water. In an oligotrophic lake, this concentration may be three orders of magnitude lower than that present in river water (Baughman and Lassiter, 1978). Therefore, biodegradation may not be a significant process in such aquatic systems.

The rate of hydrolysis of methyl parathion in aquatic media has been studied by several investigators, and has been found to depend on both the pH and the temperature of water bodies. Higher temperatures and higher pH values tend to increase the rate of hydrolysis. The hydrolytic half-life for methyl parathion in freshwater has been estimated to be 72-89 days at a pH of <8 and a temperature of 25°C (Mabey and Mill, 1978; Smith et al., 1978). The hydrolytic half-life was estimated to be ~188 days in seawater, at an average pH of 8.3 and a temperature of 4°C (Wade, 1979). With natural freshwater of pH 6-8 and a temperature of 40°C, Smith et al. (1978) estimated the hydrolytic half-life value for methyl parathion to be 8 days.

The probability of direct photolysis for methyl parathion was considered by Smith et al. (1978). With five natural water samples of pH 5-6 and a temperature of 28°C, these authors estimated the photolytic half-life of methyl parathion to be 8 days during the summer period and 38 days during the winter period. Thus, photolysis could be a significant fate-determining process of methyl parathion in bodies of water when the light attenuation effect is minimal.

No information pertaining to the significance of free radicals ($RO_2\cdot$, $RO\cdot$, etc.) in determining the fate of methyl parathion in aquatic media was available in the literature.

The loss of methyl parathion through physical transport processes, such as volatilization in aquatic media, should also be considered in predicting the aquatic fate of this chemical. The reaeration rate ratio ($K_v^C/K_v^O$, where $K_v^C$ is the rate of volatilization from water and $K_v^O$ is the rate of aeration into water) at 15°C for methyl parathion has been estimated to be 0.008 (Metcalfe et al., 1980). Assuming that the oxygen reaeration rates ($K_v^O$) in representative bodies of water vary from 0.19-0.96 $day^{-1}$ (Mabey et al., 1981), the half-life for evaporation from water can be calculated to be 90-456 days. Therefore, volatilization may not be a significant fate determining process for methyl parathion in aquatic media.

The possibility of methyl parathion removal in aquatic media through sorption and subsequent precipitation was studied by Baughman and Lassiter (1978). These authors used a simple mathematical model known as EXAMS to predict the fate of a chemical in bodies of water. According to the results derived from this model, adsorption ranked next to biodegradation in order of importance for the removal of methyl parathion from pond waters. In an oligotrophic lake, the rate of methyl parathion removal through sorption was slower than both photolysis and hydrolysis.

Relative contributions of these different processes to the overall environmental fate of methyl parathion will vary greatly depending on conditions, with the process of the shortest half-life dominating. In a pond, the order of importance is biodegradation, adsorption, hydrolysis and photolysis whereas the reverse order prevails in an oligotrophic lake (Baughman and Lassiter, 1978). In a study by Crossland and Elgar (1983), the observed rate of loss of methyl parathion from water was greater than that predicted from a mathematical modelling, possibly due to hydrolysis catalyzed by sediment or to biodegradation. The overall half-life for methyl parathion in freshwater can be estimated to be 3-4 days from the investigations of Wauchope and Leonard (1980) and Eichelberger and Lichtenberg (1971). The half-life for methyl parathion in seawater at 27°C was estimated to be 22 days (Wade, 1979). Walker (1981), however, using a screening test, estimated the average half-life of methyl parathion to be ~37 days in bay water and 14 days in sediment from bay water.

No measured steady-state BCF for methyl parathion in aquatic organisms is available. Using correlation equations, Kenaga (1980) estimated the BCF for this compound from its water solubility and $K_{oc}$ value. The estimated log BCF value ranged from 1.80-2.89. Therefore, this compound may not significantly bioconcentrate in aquatic organisms.

## 2.2. SOILS

Methyl parathion undergoes degradation processes in soils similar to those described for this compound in aquatic media. When present in soils at reasonable levels (<100 ppm concentration), methyl parathion degrades rather rapidly (Sanborn et al., 1977). Under conditions of bulk disposal, however, the degradation is significantly retarded (Sanborn et al., 1977).

Butler et al. (1981) observed only 57% degradation of methyl parathion in 1 year subsequent to a simulated soil spill (initial soil concentration of 48,900 ppm). Davidson et al. (1980) observed only 0.1% degradation of methyl parathion in 52 days at a soil concentration of 10,015 ppm. At a soil concentration of 24.5 ppm, however, >50% of the compound degraded in 10 days (Davidson et al., 1980).

The loss of methyl parathion from soil can occur through chemical, microbiological and physical processes. The possibility and relative significance of these processes in determining the fate of this compound are discussed below.

Although this compound degraded rapidly from coated glass plates (59% loss in 8 hours) when irradiated with light of wavelength 300-400 nm (Baker and Applegate, 1974), only 5-17% of decomposition in 50-60 days was attributable to photochemical reactions when the compound was present in soils (Baker and Applegate, 1970). Assuming an average of 10% degradation in 50 days due to photochemical reactions, the half-life for photodecomposition would be ~330 days. Thus, photodecomposition in soil does not appear to be a significant loss mechanism for methyl parathion.

The effect of temperature on the loss of methyl parathion in soils was studied by Baker and Applegate (1970). These investigators observed losses of methyl parathion of ~46-48% and 64-65% at 30°C and 50°C, respectively, in 50 days. Since analysis of soil extracts revealed no degradation products of methyl parathion, it is not clear whether the effect of temperature was thermal degradation (with the formation of volatile products) or volatilization of the intact molecule. In view of the observation that only 0.25-2.6% volatilization of the compound was observed in 29 days at 25°C (Spencer et al., 1979), volatilization from soils may not be a significant fate process for methyl parathion.

Temperature and pH-dependent hydrolysis of methyl parathion may occur as it does in aqueous solutions. Its quantitative significance is difficult to assess, however, as literature provides no data on hydrolysis rates for this compound in soils.

Methyl parathion has been found to be highly biodegradable in soils (Sanborn et al., 1977). For example, both isolated microorganisms and microorganisms present in natural soil rapidly degrade methyl parathion, with 99.9% degradation in soil occurring in ~3 weeks (Sanborn et al., 1977). Spencer et al. (1979) also found 97-99.5% degradation of methyl parathion in 33 days, evidently through biodegradation. It has been demonstrated by Adhya et al. (1981) that microbial degradation is more rapid under anaerobic than aerobic conditions. Thus, this process is likely to be the most significant degradation mechanism for methyl parathion.

The loss of methyl parathion from soils through physical processes, such as volatilization, runoff and leaching, is also possible. The potential for methyl parathion loss through runoff is low (Wauchope and Leonard, 1980). The leachability of methyl parathion in soils is dependent on soil characteristics such as the organic matter content. The $K_{oc}$ values for methyl parathion in different soils have been given in Section 1.2. In soils high in organic matter, methyl parathion may undergo considerable degradation before the compound has a chance to leach into groundwater. In one study, methyl parathion was found not to penetrate below 70 cm of soil, 1.5 years after application (Molozhanova, 1980). However, methyl parathion may leach into groundwater from soils exposed to bulk disposal, such as accidental spill or waste disposal, particularly from soils with low sorption capacity.

Finally, the overall half-life of methyl parathion in soils under conditions of normal application has been estimated to be 6-16 days by various investigations (Sanborn et al., 1977; Davidson et al., 1980; Spencer et al., 1979).

## 2.3. AIR

Although the experiments of Gile and Gilbert (1981) and Metcalf et al. (1979) show that substantial amounts of methyl parathion may exist in the atmosphere as a result of foliage spray, no information pertaining to the fate of this compound in air is available in the literature. The experiments of Baker and Applegate (1974) on the photolysis of methyl parathion coated on glass plates indicate that photolysis of methyl parathion in air may be significant. The fate of this compound with respect to free radical reactions (e.g., OH•, O•, etc.) in the atmosphere is not known. Similarly, no information regarding the transport of this compound in air is available. It is likely that this compound will be transported from air to soil and surface water through wet and dry deposition. The intramedia transport of this compound (i.e., the distance this compound may travel through the air from one region to another) will largely depend on the lifetime in air.

## 3. EXPOSURE

Stanley et al. (1971) monitored the atmosphere of Stoneville, MS, Orlando, FL, and Dothan, AL, from August, 1967 to August, 1968, and found maximum levels of methyl parathion of 129, 5.4 and 29.6 ng/m³, respectively, in 24-hour composited samples. Arthur et al. (1976) monitored the atmospheric levels of methyl parathion at Stoneville, MS, from 1972-1974. The average monthly level was 32.8, 80.4 and 46.3 ng/m³ for the years 1972, 1973 and 1974, respectively. During each of the 3 years, the monthly level of methyl parathion peaked in August or September, ranging from 112-791 ng/m³.

The atmospheric level of methyl parathion in a tobacco field at Raleigh, NC, soon after application of the pesticide in either emulsifiable (EC) or microencapusulated (ENCAP) form was studied by Jackson and Lewis (1978). On day 0, the respective atmospheric levels from EC and ENCAP were 7400 ng/m³ and 3800 ng/m³. By day 9, the levels had fallen to 13 and 16 ng/m³ from EC and ENCAP application, respectively.

The level of methyl parathion in the indoor and outdoor air of pesticide formulators was measured by Tessari and Spencer (1971). The method consisted of exposing nylon chiffon cloth screen to the atmosphere for 5 days and analyzing the collected methyl parathion. The ranges of methyl parathion in the indoor and outdoor air were 0.04-9.40 and 0.15-0.71 μg/m², respectively.

Pfaender et al. (1977) monitored 10 sites in the Cape Fear River Basin, NC, from July 1974 to June, 1975, and reported methyl parathion concentrations in whole water ranging from none detected to 468 ng/ℓ. The dissolved fraction contained an average of 20.2 ng/ℓ, while the particulate fraction contained an average of 5.8 ng/ℓ. The STORET data base (see

Appendix) contains a large amount of monitoring data for methyl parathion from a total of 6146 sites. The gross analysis of these data is given in Table 3-1.

The analysis of tapwater in Ottawa, Ontario by LaBel et al. (1979) showed no detectable level of methyl parathion at a detection limit of 1 ng/ℓ.

Butler and Schutzmann (1978) reported methyl parathion levels of ≤47 ng/g in various species of juvenile estuarine fish in 21 coastal states during 1972-1976. Wicker et al. (1979) reported a level of 0.13-0.14 $\mu g/cm^2$ methyl parathion in the outer shuck of sweet corn harvested 1 or 2 days after application of the pesticide. The inner shuck, however, did not contain any detectable level of the pesticide.

It is difficult to estimate the human intake of methyl parathion through inhalation and ingestion. All the reported levels of methyl parathion in the atmosphere are from sites surrounding the agricultural areas where the pesticide had been used. Similarly, evaluation of methyl parathion exposure to the general United States population through food and drinking water would require much more monitoring data than are presently available in the literature.

TABLE 3-1

Monitoring Data for Methyl Parathion

| | Whole Water (µg/ℓ) | Mud (µg/kg) | Filtered Fraction (µg/ℓ) | Suspended Fraction (µg/ℓ) | Fish (wet weight) (mg/kg) |
|---|---|---|---|---|---|
| Number of observations | 28,140 | 6012 | 544 | 202 | 239 |
| Maximum | 400 | 500 | 0.1 | 0.01 | 0.271 |
| Minimum | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Mean | 0.063 | 2.88 | 0.001 | 0.00005 | 0.016 |

# 4. PHARMACOKINETICS

## 4.1. ABSORPTION

Methyl parathion is absorbed by animals following ingestion, inhalation or dermal exposure as evidenced by the inhibition of cholinesterase activity observed following treatment by these routes (Chapter 5). Good GI absorption of methyl parathion by dogs was observed following oral dosing by gavage with 3 mg/kg of $^{35}$S-methyl parathion in ethanol (3 mL) (Braeckman et al., 1983). The two dogs excreted 63 and 74% of the dose in the urine over 6 days. When the same two dogs were treated i.v. with an identical dose of $^{35}$S-methyl parathion (following a recovery period), 80 and 96% of the dose, respectively, was excreted in the 6-day urine. By dividing the percent excretion following oral dosing by the percent excretion following i.v. dosing, it was calculated that 79 and 77% of the dose was absorbed from the GI tracts of the two respective dogs. Although there was a large amount of individual variability, lower blood levels of methyl parathion in four dogs were reached after oral dosing at 20 mg/kg $^{35}$S-methyl parathion than after i.v. dosing at 20 mg/kg $^{35}$S-methyl parathion (Willems et al., 1980a,b; Braeckman et al., 1983). Only a fraction of the oral dose reached the systemic circulation, suggesting extensive uptake by the liver in the first pass.

In a series of experiments designed to establish field re-entry interval for agricultural workers, human subjects entered a cotton field that had been sprayed with methyl parathion (Ware et al., 1973, 1974, 1975). In the first study, two subjects entered the field 3 minutes, 12, 24, 48 and 72 hours after the application of 1 lb methyl parathion/acre for periods of 30 minutes, during which time they collected leaf samples by hand (Ware et al., 1973). Serum levels of methyl parathion were 27 and 32 ppb, 24 hours after

the last exposure. The investigators concluded that the major route of absorption was via the unprotected hands. Since at 4 hours after application the atmospheric levels were 0.03-0.05 μg/ft³ (~1.06-1.77 μg/m³), inhalation exposure was minimal. In the next study, four human subjects entered the cotton field 24 hours after treatment with methyl parathion (1 lb/acre) for a 5-hour period (Ware et al., 1974). No methyl parathion residues were detected in serum at 2 hours during exposure or immediately after exposure; however, the four men excreted an average of 1.98 mg of para-nitrophenol in the 48-hour urine. In the third study, five men entered the cotton field 12 hours after application of methyl parathion (1 lb/acre) for 5 hours (Ware et al., 1975). At 3 hours during, 2 hours post-, and 24 hours post-exposure, serum levels of methyl parathion averaged 156, 101.4 and 2.4 ppb, respectively.

## 4.2. DISTRIBUTION

Miyamoto (1964) studied the distribution of methyl parathion and metabolites in male rats and male guinea pigs following i.v. injection with $^{32}P$-methyl parathion. The animals were treated at doses of 20 or 40 mg/kg methyl parathion for guinea pigs and 15 mg/kg for rats. The distribution of residues of methyl parathion and methyl paraoxon at 2.5 minutes after the three treatments is presented in Table 4-1. Methyl parathion was rapidly and widely distributed to the tissues of the bodies of rats and guinea pigs, with relatively high levels of $^{32}P$ detected in brain, liver, heart, lungs and kidneys of both species.

Willems et al. (1980b) tested the hypothesis that the liver extracts a considerable amount of orally administered methyl parathion in the first pass from the portal system, preventing the majority of the ingested pesticide from entering the systemic circulation. An extraction ratio of 90% was

0581D

TABLE 4-1

Distribution of $^{32}P$ in the Tissues of Rats and Guinea Pigs, 2.5 Minutes After Intravenous Injection of $^{32}P$-Methyl Parathion*

(Results Expressed as µg Equivalents of Methyl Parathion/g Tissue)

| | Rat (15 mg/kg) | | | Guinea Pig (20 mg/kg) | | | Guinea Pig (40 mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Methyl Parathion | Methyl Paraoxon | Total | Methyl Parathion | Methyl Paraoxon | Total | Methyl Parathion | Methyl Paraoxon |
| Brain | 19.8 | 18.9 | 0.02 | 35.6 | 26.6 | 0.01 | 74.4 | 59.6 | 0.11 |
| Liver | 22.7 | 3.0 | 1.80 | 43.5 | 8.4 | 0.55 | 63.6 | 25.5 | 1.77 |
| Lung | 17.3 | 16.8 | 0.24 | 66.4 | 56.3 | 1.18 | 205.0 | 82.8 | 2.97 |
| Heart | 16.1 | 12.5 | 0.19 | 35.0 | 27.4 | 0.11 | 108.1 | 93.6 | 0.19 |
| Kidney | 19.1 | 7.1 | 0.05 | 46.7 | 18.1 | 0.09 | 93.6 | 57.8 | 0.51 |
| Spleen | 8.3 | 5.3 | 0.02 | 28.2 | 15.4 | 0.08 | 46.7 | 36.1 | 0.01 |
| Muscle | 8.6 | 5.2 | 0.09 | 8.3 | 4.6 | 0.04 | 17.5 | 10.3 | 0.09 |
| Blood | 9.5 | 6.6 | 0.38 | 15.8 | 11.6 | 0.53 | 33.4 | 25.7 | 0.67 |

*Source: Miyamoto (1964)



08/27/84

obtained when 1.15 mg methyl parathion was added to the recirculation perfusate (bovine RBCs, 2% albumin and Krebs-Henseleit solution) of isolated rat liver.

Braeckman et al. (1983) injected five anesthetized dogs with methyl parathion i.v. at a dose of 20 mg/kg and compared the levels of methyl parathion in the female artery and the hepatic vein over 2 hours. Considerably lower levels were found in the hepatic vein than in the hepatic artery, indicating extensive hepatic extraction. The calculated hepatic extraction ranged from 63-97% of the dose.

In vitro binding of methyl parathion to dog and human serum and a solution of human albumin was >90% when tested at concentrations of 0.2-30 µg/mℓ (Braekman et al. 1983).

Ackermann and Engst (1970) studied the distribution of methyl parathion in maternal and fetal tissues 30 minutes after an oral dose of methyl parathion in ethanol of 11.1 mg/kg to four pregnant rats, 1-3 days before parturition. Fetal brain, liver and muscle, and maternal liver and placenta contained detectable concentrations of methyl parathion, demonstrating the transplacental transfer of the pesticide.

## 4.3. METABOLISM

The metabolism of methyl parathion in animals has been well-characterized, and an overall scheme was presented by Benke and Murphy (1975). Microsomal oxidation and microsomal degradation of methyl parathion both require NADPH and oxygen. The oxidation results in the activation of methyl parathion to the anticholinesterase oxygen analog, methyl paraoxon. The microsomal, oxidative degradation of methyl parathion results in detoxification to para-nitrophenol and dimethyl phosphorothioic acid. Two other detoxification reactions involve the GSH-dependent methyl transferase and

para-nitrophenyl transferase to yield the demethylated metabolite O-methyl-O-para-nitrophenyl phosphorothioate, and dimethyl phosphorothioic acid, respectively, along with the respective GS-conjugate. Similar reactions demethylate and dearylate methyl paraoxon to O-methyl-O-para-nitrophenyl phosphate and dimethyl phosphate, respectively. Enzymatic hydrolysis of methyl paraoxon to yield phosphoric acid and paranitrophenol is an additional detoxification mechanism.

Numerous investigators have studied various aspects of the metabolic scheme; however, time constraints preclude an extensive discussion of these studies. Studies that have contributed to the elucidation of the metabolic pathway include: Miyamoto (1964); Fukami and Shishido (1966); Johnsen and Dahm (1966); Hollingworth et al. (1967); Nakatsugawa et al. (1968); Rao and McKinley (1969); Benke et al. (1974). More recent studies have been concerned with the effects of metabolic modifiers in activation and detoxification (Levine and Murphy, 1977), and comparison of metabolism of methyl parathion and other organophosphorus compounds (Yamamoto et al., 1983).

Morgan et al. (1977) detected para-nitrophenol and dimethylphosphate in the urine of four human volunteers who had ingested 2 or 5 mg methyl parathion/day for 5 days.

## 4.4. EXCRETION

Hollingworth et al. (1967) studied the excretion of metabolites of methyl parathion in the urine of mice following oral administration of $^{32}$P-methyl parathion. Urinary excretion of radioactivity was rapid, with ~55 and 75% of the 17 and 3 mg/kg doses, respectively, eliminated in <18 hours. A total of 75% of the high-dose and 80% of the low-dose had been eliminated in 54-72 hours. Fecal excretion amounted to 5-10% of the administered dose.

Braeckman et al. (1980) administered methyl parathion to dogs i.v. at doses of 1, 3, 10 or 30 mg/kg and followed the time-course of elimination from serum. Based on a kinetic analysis of the data, 2- or 3-compartment models were proposed. Serum levels of methyl parathion declined rapidly within the first 2 hours after dosing and then fell slowly. The mean half-life of the terminal phase in 5 of 6 dogs at the 10 mg/kg dose was 7.2 hours. The data from two of the dogs best fit a 3-compartment model (with a central, a deep peripheral and a shallow peripheral compartment), while the data from four of the dogs best fit the 2-compartment model (central and peripheral compartment model). The model predicted that 50% of the dose would be eliminated in 5 hours, while the remaining methyl parathion would be located in the peripheral compartments and be eliminated more slowly.

The urinary excretion of para-nitrophenol and dimethyl phosphate by human volunteers was studied by Morgan et al. (1977). The four men had ingested 2 or 4 mg of methyl paration daily for 5 days. The average 24-hour urinary recoveries of para-nitrophenol and dimethylphosphate were 27 and 12% of the dose, respectively. Maximum urinary excretion of para-nitrophenol occurred within 4 hours of dosing, while peak elimination of dimethylphosphate occurred between 4 and 8 hours after dosing.

## 5. EFFECTS

### 5.1. CARCINOGENICITY

In an NCI (1979) bioassay of carcinogenicity, groups of 50 male and 50 female Fischer 344 rats, 6 weeks of age at the start of the test, were maintained on diets containing methyl parathion for 105 weeks. The low- and high-dose levels, 20 and 40 ppm, were determined from a preliminary subchronic test. Matched controls consisted of 20 rats of each sex that were maintained on the basal diet. No treatment-related increased mortality was observed for male rats or low-dose female rats; however, high-dose females had increased mortality (54%) compared with controls (5%). Comprehensive gross and histological examinations were performed on all rats killed at the end of the experiment and rats that died spontaneously, except when autolysis and/or cannibalism precluded examination. No treatment-related increased incidence of tumors was found.

Groups of 50 male and 50 female B6C3$F_1$ mice (6 weeks of age at the start) were given methyl parathion in the diet for 102 weeks (NCI, 1979). The control groups contained 20 mice of each sex. The low- and high-dose levels, 62.5 and 120 ppm, respectively, were determined from a preliminary subchronic study. Female mice were maintained at these dietary levels throughout the study period. Reduced mean body weight gain was observed in low- and high-dose male groups; therefore, the dose levels were lowered to 20 and 50 ppm, respectively, at 38 weeks, resulting in TWA doses of 35 and 77 ppm, respectively. No significant differences in mortality were observed among the treated and control groups. Comprehensive gross and histologic examination of all mice that were killed at the end of the study or that died spontaneously (except when precluded by autolysis or cannibalism) revealed no treatment-related increased incidence of tumors among the groups.

The results of this study were also reported in a separate publication by Weisburger (1982).

## 5.2. MUTAGENICITY

Methyl parathion has been tested in numerous mutagenicity and genotoxicity assays in prokaryotic and eukaryotic systems with equivocal results. These studies are summarized in Tables 5-1 and 5-2.

When methyl parathion was tested for reverse mutation by plate incorporation or the spot test in at least six strains of Salmonella typhimurium, negative results were reported in the presence (Waters et al., 1982) and absence (Waters et al., 1982; Carere et al., 1978) of the S-9 metabolic activating system; however, in an abstract by Ercegovich and Rashid (1977), it was implied that the response for methyl parathion was weakly positive in the absence of S-9 and more active in the presence of an activation system. Negative responses were obtained in Escherichia coli for reverse mutation with and without metabolic activation using the spot test (Dean, 1972) or plate incorporation application technique (Waters et al., 1982). Methyl parathion was negative for forward mutation in Streptomyces coelicolor (Carere et al., 1978), for differential toxicity in S. typhimurium strains SL4525 ($rec^+$) and SL4700 ($rec^-$), and resulted in ambiguous responses in E. coli strains W3110 (pol $A^+$) and P3478 (pol $A^-$), and in Bacillus subtilis strains H17 ($rec^+$) and M45 ($rec^-$) (Waters et al., 1982). A positive response was obtained for DNA breakage when methyl parathion was incubated with $^3$H-DNA from E. coli strain K-12 (Col E/plasmid DNA) (Griffin and Hill, 1978)

Methyl parathion treatment resulted in negative responses, with or without metabolic activation, in assays involving point gene mutations in eukaryotic systems: reverse mutation in Saccharomyces cerevisiae diploid

TABLE 5-1

Mutagenicity Testing of Methyl Parathion in Prokaryotic Systems

| Assay | Indicator/Organism | Purity | Application | Concentration or Dose | Activating System | Response | Reference |
|---|---|---|---|---|---|---|---|
| Reverse mutation | Salmonella typhimurium TA1535, TA1536 TA1537, TA1538 | NR | spot test | NR | none | - | Carere et al., 1978 |
| Reverse mutation | S. typhimurium 5 strains (NOS) | NR | NR | NR | ±S-9 | +* | Ercegovich and Rashid, 1977 |
| Reverse mutation | S. typhimurium TA1535, TA1537 TA98, TA100 | technical grade | plate incorporation | 6 concentrations ≤10 mg/plate | ±S-9 | -<br>- | Waters et al., 1982 |
| Reverse mutation | Escherichia coli WP2 | NR | spot test | NR | none | - | Dean, 1972 |
| Reverse mutation | E. coli WP2 | technical grade | plate incorporation | 6 concentrations ≤10 mg/plate | ±S-9 | -<br>- | Waters et al., 1982 |
| Forward mutation | Streptomyces coelicolor | NR | spot test | NR | none | - | Carere et al., 1978 |
| Differential toxicity | S. typhimurium SL4[illegible]-rec⁺) SL4700(rec⁻) | technical grade | spot test | NR | none | - | Waters et al., 1982 |
| Differential toxicity | E. coli W3110(pol A⁺) P3478(pol A⁻) | technical grade | spot test | NR | none | NT | Waters et al., 1982 |
| Differential toxicity | Bacillus subtilis H17(rec⁺) M45(rec⁻) | technical grade | spot test | NR | none | NT | Waters et al., 1982 |
| DNA damage | E. coli K-12 Col E/plasmid DNA | NR | In vitro incubation with ³H-DNA | 0.1 mg/mL | none | + | Griffin and Hill, 1978 |

*The authors implied that methyl parathion was weakly mutagenic in the absence of S-9 and stated that the response was considerably greater in the presence of S-9.

NR = Not reported; NOS = not otherwise specified; NT = no test (ambiguous results)



0581p

08/27/84

TABLE 5-2

Mutagenicity Testing of Methyl Parathion in Eukaryotic Systems

| Assay | Indicator/Organism | Purity | Application | Concentration or Dose | Activating System | Response | Reference |
|---|---|---|---|---|---|---|---|
| Reverse mutation | Saccharomyces cerevisiae D7 | technical grade | plate incorporation | 5 concentrations ≤10 mg/plate | ±S-9 | -<br>- | Waters et al., 1982 |
| Forward mutation | S. cerevisiae D7 | NR | NR | NR | ±S-9 | -<br>- | Riccio et al., 1981 |
| Forward mutation | Schizosaccharomyces pombe haploid strain | NR | cell incubation | 11-220 mM | ±S-9 | -<br>- | Gilot-Delhalle et al., 1983 |
| Forward mutation | mouse lymphoma cells, L5178 | technical grade | cell culture | NR | ±S-9 | +[a] | Waters et al., 1982 |
| Recessive lethal | Drosophila melanogaster | technical grade | exposure of males | NR | NA | - | Waters et al., 1982 |
| Mitotic recombination | S. cerevisiae D3 | NR | NR | NR | ±S-9 | -<br>- | Riccio et al., 1981 |
| Mitotic recombination | S. cerevisiae D3 | technical grade | plate incorporation | 5 concentrations | ±S-9 | +[a] | Waters et al., 1982 |
| Mitotic crossover | S. cerevisiae D7 | NR | NR | NR | ±S-9 | -<br>- | Riccio et al., 1981 |
| Mitotic crossover and gene conversion | S. cerevisiae D7 | technical grade | spot test | 5 concentrations | ±S-9 | -<br>- | Waters et al., 1982 |
| Mitotic gene conversion | S. cerevisiae D7 | NR | NR | NR | ±S-9 | -<br>- | Riccio et al., 1981 |
| Mitotic gene conversion | S. cerevisiae D7 | NR | liquid holding test | 114 mM | NR | + | Fahrig, 1974 |
| Unscheduled DNA synthesis | human lung fibroblasts | technical grade | cell incubation | 5 concentrations (NOS) | ±S-9 | -<br>- | Waters et al., 1982 |
| Sister chromatid exchange | Chinese hamster V79 cells | 96.8% | cell culture | 0-40 µg/ml | none | +[b] | Chen et al., 1981 |
| Sister chromatid exchange | Chinese hamster ovary cells | technical grade | cell incubation | 5 concentrations (NOS) | ±S-9 | +<br>- | Waters et al., 1982 |



0561p
08/27/84

TABLE 5-2 (cont.)

| Assay | Indicator/Organism | Purity | Application | Concentration or Dose | Activating System | Response | Reference |
|---|---|---|---|---|---|---|---|
| Sister chromatid exchange | human lymphoid cell line LAZ-007 | NR | cell culture | 0.02-20 µg/mL | none | +[c] | Sobti et al., 1982 |
| Sister chromatid exchange | human lymphocytes (normal) | 96.8% | cell culture | 0-40 µg/mL | none | + | Chen et al., 1981 |
| Sister chromatid exchange | Burkitt lymphoma cells 835M | 96.6% | cell culture | 0-40 µg/mL | none | + | Chen et al., 1981 |
| Chromosome damage | human hematopoietic cells, RPMI 1788, 7191 and 8411-4 | 98% | cell culture | 0, 25, 50, 75, 100 µg/mL | none | -[d] | Huang, 1973 |
| Chromosome damage | mouse bone marrow cells | 98% | i.p. injection | 0, 5, 10, 20, 100 mg/kg | NA | -[e] | Huang, 1973 |
| Chromosome aberrations | mouse bone marrow and spermatogonia | NR | drinking water of male mice | 0.026 mg/kg/day 7 days | NA | - | Degraeve et al., 1982 |
| Dominant lethal | mouse | NR | in vivo route NR | 10 mg/kg | NA | - | Degraeve et al., 1979 |
| Dominant lethal | mouse | NR | drinking water | 0.026 mg/kg/day 7 days | NA | - | Degraeve et al., 1982 |
| Dominant lethal | mouse | NR | diet | 3 concentrations (NOS) for 7 days | NA | - | Jorgensen et al., 1976 |
| Dominant lethal | ICR/Swiss mouse | technical grade | diet | 0.25 MTD, 0.5 MTD, or MTD[f] | NA | - | Waters et al., 1982 |

[a]The response was positive in the absence of S-9; results for the assay in the presence of S-9 were not reported.

[b]Dose-related increase in response with 2-3x greater than control sister chromatid exchange/cell at 40 µg/mL. In a subsequent study (Chen et al., 1982), the induction of sister chromatid exchange was decreased by S-9.

[c]Significantly increased response at 2 and 20 µg/mL ($p<0.01$).

[d]Cell growth was inhibited dose-relatedly.

[e]Doses of 50 or 100 mg/kg were fatal. Negative for chromosome aberrations <20 mg/kg.

[f]MTD = Maximum tolerated dose or 5 g/kg, whichever was lower; defined as the dose that resulted in 20% body weight loss and mild clinical signs but not increased mortality or reproductive impairment.

NR = Not reported; NA = not applicable; NOS = not otherwise specified

strain D7 (Waters et al., 1982), forward mutation in S. cerevisiae D7 (Riccio et al., 1981) and Schizosaccharomyces pombe haploid strain (Gilot-Delhalle et al., 1983), and the recessive lethal assay in Drosophila melanogaster (Waters et al., 1982). However, methyl parathion was positive without metabolic activation for reverse mutation in cultured mouse lymphoma cells (Waters et al., 1982).

Equivocal results have been obtained when methyl parathion was tested for DNA damage in eukaryotic systems: the mitotic recombination response in S. cerevisiae haploid strain D3 was reported to be negative in the presence and absence of S-9 by Riccio et al. (1981), and positive in the absence of S-9 by Waters et al. (1982); the response for mitotic cross-over and gene conversion in S. cerevisiae D7 was reported as negative by Waters et al. (1982) and Riccio et al. (1981), and as positive by Fahrig (1974). Methyl parathion was negative for unscheduled DNA synthesis in cultured human lung fibroblasts (Waters et al., 1982).

Results of testing methyl parathion in assays involving effects on chromosomes have also been contradictory. For sister chromatid exchange, Waters et al. (1982) reported a positive response in Chinese hamster ovary cells in the presence but not in the absence of S-9, while methyl parathion was positive without activation in cultured normal human lymphoid cells (Sobti et al., 1982; Chen et al., 1981) and in Burkitt lymphoma cells (Chen et al., 1981). Negative results were obtained for chromosome damage in cultured human hematopoietic cells (Huang, 1973), and in mouse bone marrow cells from mice treated with methyl parathion (Huang, 1973; Degraeve et al., 1982). Methyl parathion treatment in male mice did not increase the incidence of resorbed fetuses in mated dams (Degraeve et al., 1979, 1982; Jorgensen et al., 1976; Waters et al., 1982).

De Cassia et al. (1982) found no increase in the percentage of lymphocyte cells with chromosome breaks in 15 pesticide plant workers who were exposed to methyl parathion for 0.4-91 months when compared with 13 non-exposed controls.

## 5.3. TERATOGENICITY

Crowder et al. (1980) administered methyl parathion (99.9% pure) in corn oil to three pregnant Sprague-Dawley rats at a daily oral dose of 1.0 mg/kg bw on days 7-15 of gestation. Another group of three rats received only corn oil; dams were allowed to deliver. Mortality of pups born to exposed dams was 30% compared with 10% in control pups. Rat pups were tested for learning ability (2-choice maze), motor skills and behavioral effects. Methyl parathion exposure did not appear to have an effect on righting, starting or placement reflexes; however, differences in emotionality (measured by movement around an open field and increased defecation) were observed in the treated group compared with controls. Methyl parathion exposed pups had significant differences ($p<0.05$) from controls in maze learning time.

As reviewed by IARC (1983) and reported in an abstract of a German study, Fuchs et al. (1976) treated pregnant rats with oral doses of methyl parathion as follows. On 6 alternate days between days 5 and 15 of gestation, some rats received 0.1, 1 or 3 mg/kg bw; on 8 alternate days between day 5 and 19 of gestation, another group was treated at 3 mg methyl parathion/kg bw. Increased resorptions and decreased fetal body weight were observed in the rats treated with 3 mg/kg bw, regardless of dose schedule. No fetal malformations were observed, and no significant differences from controls were observed at lower doses. Further details were not reported.

Gupta et al. (1983) treated pregnant rats with daily oral doses of methyl parathion in peanut butter/oil at 1.0 or 1.5 mg/kg bw from days 6-15 or 6-19 of gestation. On the last day of treatment, dams were injected s.c. with $^{14}$C-valine and sacrificed within 2 hours; protein synthesis was measured. A dose-related increased inhibition of $^{14}$C-valine in protein was observed in maternal brain, viscera, placenta and whole embryos (in rats sacrificed on day 15) and in fetal brain and viscera (rats sacrificed on day 19). The inhibition was greater in the rats killed on day 19 and more pronounced in the tissues of fetuses than in tissues of dams. Further details were not reported in the abstract.

Pregnant Holzmann rats were treated i.p. with methyl parathion in ethanol:propylene glycol (20:80) at 4.0 mg/kg bw on day 9 or 15 of gestation (day 0 = day on which sperm were observed in vaginal smears) or at 6.0 mg/kg bw on day 9 of gestation (Fish, 1966). Controls were treated with vehicle on day 9 of gestation. Signs of cholinesterase inhibition were observed in treated dams within 5-10 minutes of methyl parathion injection, but subsided in 4-6 hours in surviving dams. The investigator stated that maternal deaths usually occurred within 30 minutes of treatment; however, no data on original number of rats or incidence of mortality were reported. Vehicle-treated controls had drowsiness and slight ataxia, conditions that the investigator attributed to ethanol treatment. Dams were found to have depressed RBC cholinesterase levels when blood samples were taken at 4 and 20 hours after treatment. Some of the dams were killed on day 21 of gestation; others were allowed to deliver naturally. Reduced cerebral cortical cholinesterase activity was observed in all fetuses from treated dams. No treatment-related effects were observed with respect to number or size of litters or fetal body weight. There were no gross fetal abnormalities or

mortality. For the litters that delivered at term, there were no differences in litter numbers or size, mortality, or average body weight of pups, and there were no gross abnormalities.

Tanimura et al. (1967) treated pregnant Wistar rats and pregnant ICR-JCL mice i.p. with methyl parathion on day 12 and day 10 of gestation, respectively (day 0 was defined as the day on which evidence of mating was observed). Rats were treated with methyl parathion in an aqueous solution of sodium carboxymethyl cellulose at doses of 5, 10 or 15 mg/kg/bw, while mice were treated at 20 or 60 mg/kg/bw. The controls were treated with vehicle. Signs of cholinesterase inhibition appeared in treated dams within 30 minutes of dosing, and several dams died within 2 hours. Surviving dams had dose-related reduced food consumption and reduced body weight that persisted for 3 or 4 days after dosing. Rats were killed on day 21 of gestation. There were no treatment-related effects with respect to number and size of litters or fetal mortality. Mean fetal body weight was significantly ($p \leq 0.05$) reduced in the 15 mg/kg group when compared with control. There were no external or internal teratogenic or skeletal defects; however, delayed ossification of caudal vertebrae in the high-dose group was observed. The pregnant mice were killed on day 18 of gestation. Fetal mortality in the 60 mg/kg group (22.3%) was significantly increased ($p \leq 0.05$) when compared with control (2.9%). The 20 mg/kg group had 4.2% mortality. The incidence of cleft palate, the only observed teratogenic malformation, was 0% in controls, 1.5% in the low-dose group and 14.9% ($p \leq 0.05$) in the high-dose group. Fetal body weight was significantly reduced ($p \leq 0.05$) in the high-dose group compared with controls. No skeletal malformations were observed in the mouse fetuses; however, the high-dose group had a significantly ($p \leq 0.05$) increased incidence of cervical rib (26.7%) compared with

control (3.3%). The low-dose group had a high incidence of cervical rib (21.6%), but the increase was not statistically significantly different from control. The incidence of delayed ossification of caudal vertebrae was significantly ($p \leq 0.05$) increased above control in the high-dose group. The high doses in rats and mice were near the respective $LD_{50}$ values.

## 5.4. OTHER REPRODUCTIVE EFFECTS

Lobdell and Johnston (1966) maintained rats on diets containing 0, 10 or 30 ppm methyl parathion throughout three generations. The $F_0$ generation consisted of 10 male and 20 female rats at each dietary level. A few of the $F_0$ generation rats had tremors. Weanlings of the 30 ppm dietary level $F_{1a}$ and $F_{1b}$ generations had increased mortality compared with controls. Reproductive capacity of high-dose $F_{2b}$ females was reduced, with only 41% producing litters. The total number of stillbirths was higher in the progeny of the 30 ppm $F_{1b}$ generation compared with controls, although no significant differences in the number of stillbirths/litter between treated and control groups were observed for any mating. It was concluded that no consistent pattern of increased mortality, reduced weanling body weight or reduced reproductive performance was observed at these dietary levels of methyl parathion.

## 5.5. CHRONIC AND SUBCHRONIC TOXICITY

Only one study involving chronic exposure of animals to methyl parathion was located; however, there are numerous reports of the effects of subchronic and repeated shorter-term exposures in animals and humans.

In the previously reported carcinogenicity bioassays of methyl parathion (see Section 5.1.), F344 rats and B6C3$F_1$ mice were maintained on diets containing the pesticide for 105 and 102 weeks, respectively (NCI, 1979).

The dietary levels for rats were 0, 20 and 40 ppm. Dose-related decreases in mean body weight were observed in both sexes of treated rats throughout the study; no information on food consumption was reported, and no statistical analyses of the differences were performed. At ~97 weeks, for example, mean body weight of low- and high-dose males was ~6% lower than controls. At 98, 102 or 104 weeks, low- and high-dose females had mean body weights ~7 and 17%, respectively, below controls. High-dose females had a high rate of mortality throughout the study; at the end of the study, 54% had died spontaneously, compared with 5% of the matched female controls. The percentage of mortality at 105 weeks in other groups were ~12% for low-dose females, ~15% for control males, ~22% for low-dose males and ~22% for high-dose males. These differences in mortality, with the exception of high-dose females, were not considered to be appreciable. The results of comprehensive histological examination indicated no treatment-related increased incidence of histopathologic lesions.

For mice, the dietary levels of methyl parathion were 0, 62.5 and 125 ppm. The dietary levels for male mice were lowered to 20 and 50 ppm at weeks 38 because of decreased mean body weight gain; the TWA doses for low- and high-dose males were 35 amd 77 ppm, respectively. Decreased mean body weight compared with control (~10%) was observed for the high-dose male and female groups throughout the study. No significant dose-related trend for mortality was observed for mice. No other clinical signs of toxicity and no histopathologic lesions related to treatment were observed.

The dietary levels of methyl parathion used in the chronic NCI (1979) bioassays were determined from preliminary subchronic studies. Groups of five male and five female F344 rats were fed methyl parathion in the diet at 0, 10, 20, 30, 40 and 50 ppm for 8 weeks. No male rats died; one female rat

at each of 10, 30 and 40 ppm died, and two females at 50 ppm died. At week 7, the mean body weight of the 50 ppm males was 10% lower than controls. At the end of 8 weeks, the rats were killed; histological examination of rats at ≥30 ppm were performed, with no indication of treatment-related effects. Groups of five male and five female B6C3F$_1$ mice were fed methyl parathion in the diet at 1, 20, 40, 60, 80, 100, 125, 250 and 500 ppm. All male mice at 250 ppm and all male and female mice at 500 ppm died; one male mouse at 20 ppm died; one female at 250 ppm died. Mean body weight at 7 weeks for both sexes was increased above control (3-29%) at ≤100 ppm; at >100 ppm, mean body weight was 4-6% lower than controls. At the end of 8 weeks, the surviving mice were killed and necropsied. Mice that died spontaneously were also necropsied. Histological examination of the tissues of males and females at 125 and 250 ppm indicated no treatment-related lesions. Male and female mice at 250 and 500 ppm had rough coats and arched backs. Hemorrhage of the stomach was observed in 5/5 males at 250 ppm and 3/5 males and 5/5 females at 500 ppm.

Street and Sharma (1975) conducted an 8-week feeding study in rabbits to determine the immunosuppressive effects of methyl parathion. Groups of seven male New Zealand rabbits were maintained on diets containing methyl parathion at 0, 0.6, 2.6, 8.5 and 23 ppm for 8 weeks. Based on food consumption data, the investigators determined that these dietary concentrations corresponded to doses of 0, 0.036, 0.162, 0.519 and 1.479 mg/kg/day, respectively. Midway during the administration of methyl parathion, the rabbits were challenged with a s.c. injection of a 1:1 mixture of sheep erythrocytes and Freund's complete adjuvant. There were no outward signs of toxicity, no effects on body weight gain or food consumption, no gross lesions of visceral organs, no consistent differences in absolute weights of

liver, kidney, adrenals or spleen and no consistent differences in white cell numbers or differential white cell counts. There was no treatment-related difference in hemolysin titers, hemagglutination titers or serum gamma-globulin/transferrin ratio during the pre-antigen period or at 10, 17 or 24 days post-antigen. Methyl parathion treatment appeared to have little effect on skin sensitivity of tuberculin treated rabbits; however, there were generally dose-related reductions in the number of plasma cells that produce gamma-globulin ($p<0.05$ at $\geq 0.6$ ppm) and of germinal center counts of the spleen ($p<0.05$ at 8.5 and 23 ppm), and a dose-related increased incidence of atrophy of tissues of the thymus cortex ($p<0.05$ at 8.5 ppm).

Cholinesterase inhibition by methyl parathion was reported in a 90-day feeding study in dogs (Williams et al., 1959). Male and female (6-10 kg) mongrel dogs were maintained on diets containing 5, 20 and 50 ppm methyl parathion. Four control dogs (sexes not specified) received basal diets. Plasma and RBC cholinesterase activities were measured for 4 weeks prior to treatment, at the end of the first week, and on alternate weeks during treatment and during 8 weeks post-treatment. Values that varied in excess of twice the standard deviation of pretreatment values were considered to be significantly different. Plasma cholinesterase in the 50 and 20 ppm level dogs was significantly depressed during treatment compared with pretreatment values. The depression was dose-related; at the end of the treatment period, plasma cholinesterase activity was 55 and 75% of pretreatment values at 50 and 20 ppm, respectively. RBC cholinesterase activity also showed a dose-related decreased activity at 50 and 20 ppm that was significantly different from pretreatment activity, and as much as 50% lower than for the four nontreated control dogs. At the end of the treatment period, RBC cholinesterase activity was -58 and 62% of pretreatment values for the

50 and 20 ppm levels, respectively. At the 5 ppm level, RBC and plasma cholinesterase levels were not depressed. Other organophosphorus compounds (dipterex, Chlorthion and Diazinon) were also studied, and cholinesterase activities started to recover during treatment with these pesticides. Such was not the case with methyl parathion, since at the end of the treatment period, maximum inhibition had not been reached. Only during the post-treatment period did cholinesterase activity start to recover. The investigators suggested that methyl parathion may have greater cumulative effects compared with the other chemicals.

There are several studies from the foreign literature for which abstracts were available. In a Polish study (Cabejszek and Szulinski, 1966), daily gavage doses of methyl parathion in water at 30 µg/kg/day for 6-9 months were reported to cause a delay in the formation of conditioned reflexes to light and sound stimuli of rats. Rats (10 males, 10 females/group) ingesting drinking water containing 0.05, 0.5, 5 or 25 mg/ℓ methyl parathion had inconsistent changes in body weight gain, no treatment-related effects with respect to urinalysis and hematologic parameters and no treatment-related histopathologic lesions. In a series of studies from Bulgaria, oral doses of 0.15 and 0.75 mg/kg/day for 1, 2 or 4 months to rats were reported to result in inhibition of renal tubule succinic dehydrogenase activity and stimulation of glomerular alkaline acid phosphatase activities (Zlateva and Softova, 1977); changes in the morphology of myocardial tissue, scar tissue, focal granuloma and vascular sclerosis (Zlateva and Maleva, 1978); and increased excretion of mucus in the bronchial epithelium, chronic bronchitis, stratification of blood vessels, hyperplasia of pulmonary tissue and lymhatic atrophy (Zlateva and Gurdevski, 1978). In an abstract of a Russian study (Samedov et al., 1979), it was reported that administration of

methyl parathion in sunflower oil at 5 mg/kg bw/day, 6 days/week for 4 months to rabbits resulted in reduced phagocytic activity of white cells, reduced complement titer, decreased activity of serum lysozyme and decreased nucleic acid content of blood.

NIOSH (1976) reviewed a study from the Russian literature (Akhmedov and Danilov, 1969) in which groups of 15 rats were exposed to aerosols of methyl parathion at airborne concentrations of 0, 0.008, 0.024 and 0.072 mg/m$^3$, 24 hours/day, 7 days/week for 3 months. At the 0.072 mg/m$^3$ level, effects such as perivascular and pericellular edema, cytoplasmic vacuolization of ganglionic cells, lymphoid infiltration of heart connective tissue, necrotic changes in the liver, hyperplasia of red pulp and follicular atrophy in spleen, and atrophic and dystrophic changes in the adrenals were reported. Similar but less severe effects were noted for the 0.024 mg/m$^3$ level, and no effects were observed for the 0.008 mg/m$^3$ level. NIOSH (1976) commented on the inadequacy of the description of pathological changes. In general, the studies from the foreign literature were inadequately reported.

In a series of studies, the minimum effective dose that would result in significantly decreased RBC and/or plasma cholinesterase was determined for repeated daily doses of methyl parthion in humans (Moeller and Rider, 1959, 1961, 1962, 1963; Rider and Moeller, 1964; Rider et al., 1966, 1967, 1969, 1970, 1971). In each determination, five prisoners received methyl parathion in corn oil contained in a capsule, while two prisoners served as controls and received a capsule containing only corn oil. The determinations were conducted as follows: baseline cholinesterase activities were obtained for -30 days before treatment; methyl parathion was administered for various time periods and cholinesterase activities were measured twice weekly. No significant depression of RBC or plasma cholinesterase was

observed when methyl parathion was administered at daily oral doses up to 22.0 mg/day for ~30 days. In some determinations, the dose schedule was started at 3, 4.5, 5.5 and 6.5 mg/day for 28, 30, 28 and 35 days, respectively, followed by dosing at 3.5, 5.0, 6.0 or 7.0 mg/day for 28, 29, 29 or 24 days, respectively (Moeller and Rider, 1961, 1962). The 3 mg/day for 28 days, followed by 3.5 mg/day for 29 days schedule was followed by dosing at 4.0 mg/day for an additional 43 days. None of these treatments resulted in significantly reduced activities of cholinesterase. There were no effects on blood counts, urinalysis or prothrombin times, nor were there any outward signs of toxicity (Rider et al., 1969). Only at $\geq$24 mg/day for ~30 days were significant reductions in cholinesterase activity (20-25% below baseline activity) observed (Rider et al., 1970). At 24 mg/day, reduced RBC and plasma cholinesterase activities were observed in two of the five subjects. The mean (of 5) maximum reduction was 17% for plasma and 22% for RBC cholinesterase. At 26 mg/day, two subjects had reduced cholinesterase levels; however, the mean maximum reduction of RBC cholinesterase was only 18%. There was no change in plasma cholinesterase at 26 mg/day. At 28 mg/day, three subjects had reduced RBC cholinesterase; however, the mean maximum reduction was 19% (Rider et al., 1971). At 30 mg/day, the mean maximum reduction of RBC cholinesterase activity for the five subjects was 37%. Therefore, 30 mg methyl parathion/day for 30 days was the minimal effective dose for RBC cholinesterase inhibition.

## 5.6. OTHER RELEVANT INFORMATION

Several reported values for acute $LD_{50}$ and $LC_{50}$ of methyl parathion are presented in Table 5-3. The susceptibility of rats to methyl parathion toxicity decreased with age (Benke and Murphy, 1975; Murphy, 1982). $LD_{50}$ (i.p.) values were <1 mg/kg in neonates, ~5 mg/kg in 24-day-old rats and ~7 mg/kg in 35- to 40-day-old rats.

TABLE 5-3

Values for Acute $LD_{50}$ and $LC_{50}$ of Methyl Parathion

| Route | Species | Sex | $LD_{50}$ or $LC_{50}$ | Reference |
|---|---|---|---|---|
| Oral | rat | NR | 6 mg/kg | NIOSH, 1983 |
| Oral | rat | NR | 9.2 mg/kg | Galal et al., 1977 |
| Oral | rat | M | 14 mg/kg | Gaines, 1969 |
| Oral | rat | F | 24 mg/kg | Gaines, 1969 |
| Oral | rat | M | 12 mg/kg | Newell and Dilley, 1978 |
| Oral | rat | F | 18 mg/kg | Newell and Dilley, 1978 |
| Oral | mouse | NR | 23 mg/kg | NIOSH, 1983 |
| Oral | guinea pig | NR | 1270 mg/kg | NIOSH, 1983 |
| Oral | rabbit | NR | 420 mg/kg | NIOSH, 1983 |
| Oral | dog | NR | 90 mg/kg | Hirschelmann and Bekemeier, 1975 |
| Dermal | rat | M/F | 67 mg/kg | Gaines, 1969 |
| Dermal | rat | M | 110 mg/kg | Newell and Dilley, 1978 |
| Dermal | rat | F | 120 mg/kg | Newell and Dilley, 1978 |
| Dermal | rat | NR | 63 mg/kg | NIOSH, 1983 |
| Dermal | rabbit | NR | 300 mg/kg | NIOSH, 1983 |
| Inhalation | rat | M | 257 mg/m³-1 hour | Newell and Dilley, 1978 |
| Inhalation | rat | F | 287 mg/m³-1 hour | Newell and Dilley, 1978 |
| Inhalation | rat | NR | 120 mg/m³-4 hours | NIOSH, 1983 |

TABLE 5-3 (cont.)

| Route | Species | Sex | $LD_{50}$ or $LC_{50}$ | Reference |
|---|---|---|---|---|
| Inhalation | mouse | NR | 120 mg/m³-4 hours | NIOSH, 1983 |
| i.p. | rat | NR | 3.5 mg/kg | NIOSH, 1983 |
| i.p. | mouse | NR | 8.2 mg/kg | NIOSH, 1983 |
| s.c. | rat | NR | 6 mg/kg | NIOSH, 1983 |
| s.c. | mouse | NR | 18 mg/kg | NIOSH, 1983 |
| i.v. | rat | M | 9.0 mg/kg | Newell and Dilley, 1978 |
| i.v. | rat | F | 14.5 mg/kg | Newell and Dilley, 1978 |
| i.v. | rat | NR | 9 mg/kg | NIOSH, 1983 |
| i.v. | mouse | NR | 9.8 mg/kg | NIOSH, 1983 |
| i.v. | guinea pig | NR | 50 mg/kg | NIOSH, 1983 |

NR = Not reported

There are many reports of cholinesterase inhibition following acute exposure to methyl parathion. Yamamoto et al. (1982) observed cholinergic signs in rats treated orally with methyl parathion at 1.3, 4 or 8 mg/kg/day for up to 10 days. The two higher doses were fatal in 4 days. Following a single oral dose of methyl parathion of 13 mg/kg or repeated doses of 1.3 mg/kg/day for 10 days, brain and plasma cholinesterase activities were significantly inhibited ($p<0.05$). Brain cholinesterase activity was ~43% of control following the single dose and ~56% of control following 10 exposures to the 10-fold lower dose. Newell and Dilley (1978) reported that blood cholinesterase activity of rats was inhibited as much as 57-84% following administration of methyl parathion at or near the oral, dermal or i.v. $LD_{50}$ or $LC_{50}$ (see Table 5-3). Rats injected i.p. with methyl parathion at a dose equal to the $LD_{50}$ (not otherwise specified) had complete inhibition of acetylcholinesterase in the CNS detected by a histochemical technique (Toth et al., 1980). Myocardial cholinesterase was also inhibited. Enan et al. (1982) reported cholinesterase inhibition in the liver and brain of rats exposed orally to 0.25 $LD_{50}$ methyl parathion (not otherwise specified). Benke and Murphy (1974) found that acetylcholinesterase of brain and muscle tissue (diaphragm) of mice was inhibited to ~30% of control within 1 hour of an i.p. dose of 8 mg methyl parathion/kg. Activity was restored to 80% of control in 1-3 days. Inhibition of cholinesterase activity has also been observed in mice following dermal exposure to methyl parathion (Skinner and Kilgore, 1982a,b).

Rodnitsky et al. (1978) studied the effects of ingestion of methyl parathion on the neurobehavior and cholinesterase activity of two human volunteers. The men ingested 2 mg methyl parathion/day for 5 days; 1 or 8 weeks later, they ingested 4 mg/day for 5 days. The two men were subjected

to a battery of neurobehavioral tests (verbal recall, visual retention, information processing, linguistic competence, vigilance, etc.) before exposure and on the last day of the 4 mg/day schedule. No impairment of neurobehavior was observed, nor were plasma and RBC cholinesterase activities inhibited. It should be noted that the dose schedule was well within the no-effect range in humans observed by Rider et al. (1969, 1971).

Methyl parathion has been found to affect activities of microsomal enzymes. Uchiyama et al. (1975) found that methyl parathion at concentrations of $10^{-4}$, $10^{-5}$ and $10^{-6}$ M inhibited the in vitro activity of mouse hepatic aminopyrine N-demethylase to ~25, 34 and 83% of control, respectively. The in vitro activity of the enzyme from rat liver was ~18, 65 and 96% of control at $10^{-4}$, $10^{-5}$ and $10^{-6}$ M methyl parathion, respectively. In contrast, aminopyrine N-demethylase activity and cytochrome P-450 content of liver microsomes were not altered following methyl parathion treatment at a single oral dose of 13 mg/kg or 10 daily doses of 1.3 mg/kg/day in rats (Yamamoto et al., 1982). Methyl parathion inhibited the activity of the rat hepatic microsomal enzymes involved in its own dearylation (~73% of control) and desulfuration (~58% of control) after the repeated oral doses ($p<0.05$).

Metabolic modifiers have been shown to affect the toxicity of methyl-parathion. Mirer et al. (1977) found that piperonyl butoxide antagonized, while diethyl maleate potentiated the toxicity of methyl parathion in mice: the i.p. $LD_{50}$ (8.2 mg/kg) of methyl parathion was increased 40-fold by the 1-hour pretreatment of the mice with 400 mg piperonyl butoxide/kg, and decreased ~3.4-fold by a 1-hour pretreatment with 1 mL diethyl maleate/kg. When piperonyl butoxide and diethyl maleate were co-administered, the $LD_{50}$ was increased only ~9-fold. Phenobarbital pretreatment protected rats against the cholinergic effect of methyl parathion (Murphy, 1980).

Methyl parathion has been tested for delayed neurotoxicity in chickens. Barnes and Denz (1953) treated hens with methyl parathion by injection in three successive doses sufficient to produce severe signs of cholinesterase inhibition (not otherwise specified), and observed no paralysis during the 3-week observation period. Ohkawa et al. (1980) administered 100 mg methyl parathion/kg orally to a group of 5-10 hens. No signs of delayed neurotoxicity were observed in hens during a 4-week observation period. In hens sacrificed 2 days after treatment, brain acetylcholinesterase was 85% inhibited, while neurotoxic esterase, the inhibition of which may play a role in delayed neurotoxicity, was only 12% inhibited.

Methyl parathion was one of five organophosphate pesticides to which a female vintner with exzema had skin sensitivity (Pevny, 1980).

Methyl parathion at 10 mM inhibited the in vitro mitogenic response of human lymphocytes to phytohemagglutinin stimulation to 78.8% of control and chemotaxis of human neutrophils to 55-74% of control (Lee et al., 1979).

Electrocardiographic changes, such as bradycardia, p-wave changes, heart block, arrythmia and myocardial ischemia, were observed in rats treated with oral or dermal doses equal to the respective $LD_{50}$ and 0.5 $LD_{50}$ values (not otherwise specified) (Galal et al., 1975).

Electroretinographic effects (action on photoreceptors, synaptolytic effects, damage to bipolar neurons), detected by a silver electrode placed on the cornea of the eyes of anesthetized mice, were observed immediately following i.p. injection with methyl parathion ($LD_{50}$, not otherwise specified) (Carricaburu et al., 1980).

# 6. AQUATIC TOXICITY

## 6.1. ACUTE EFFECTS

The acute $LC_{50}$ of methyl parathion has been determined in many species of freshwater fish native to the United States (Table 6-1). The salmonids (trout and salmon) generally appear to be most sensitive, having 96-hour $LC_{50}$ values for methyl parathion in the range 1.9-5.3 mg/ℓ. Other species, however, such as the yellow perch, bluegill sunfish and largemouth bass, appear equally sensitive, with 96-hour $LC_{50}$ values within this range. To include the most resistant species, the range of 96-hour $LC_{50}$ values extended only to 12.0 mg methyl parathion/ℓ (see Table 6-1).

Johnson and Finley (1980) reported that variations of water hardness from 44-272 mg $CaCO_3$/ℓ had little effect on the toxicity of methyl parathion to rainbow trout, fathead minnows, bluegill or green sunfish. Water pH within natural ranges appeared to have little effect on toxicity (Henderson et al., 1959).

McCann and Jasper (1972) reported that methyl parathion at sublethal levels (3.9-6.9 mg/ℓ) caused vertebral hemorrhage in the caudal region of exposed bluegills. An average of 11% of the exposed fish (n=180) developed hemorrhage, the earliest visible damage occurring after 4.25 hours.

The anticholinesterase activity of methyl parathion and metabolism of the compound was examined in pumpkinseed sunfish, Lepomis gibbosus (Benke et al., 1974). Brain and muscle cholinesterases of this fish were comparably more resistant to inhibition than were mouse tissue cholinesterases. This resistance may have resulted from a slower rate of metabolism to the oxide, methyl paraoxon. The slower rate of metabolism was regarded as allowing time for glutathione conjugation and causing the observed lower toxicity of methyl parathion in fish as compared to mice (Benke et al., 1974). Chambers

TABLE 6-1

Acute Lethal Effects of Methyl Parathion to Freshwater Fish

| Species | Duration (hours) | $LC_{50}$ (mg/ℓ) | Method | Reference |
|---|---|---|---|---|
| Cutthroat trout, *Salmo clarkii* | 96 | 1.85 | static | Johnson and Finley, 1980 |
| Rainbow trout, *Salmo gairdneri* | 96 | 3.70 | static | Johnson and Finley, 1980 |
| Rainbow trout, *Salmo gairdneri* | 96 | 2.75 | static | Macek and McAllister, 1970 |
| Lake trout, *Salvelina namaycush* | 96 | 3.78 | static | Johnson and Finley, 1980 |
| Brown trout, *Salmo trutta* | 96 | 4.70 | static | Johnson and Finley, 1980 |
| Brown trout, *Salmo trutta* | 96 | 4.74 | static | Macek and McAllister, 1970 |
| Coho salmon, *Oncorhynchus kistuch* | 96 | 5.30 | static | Macek and McAllister, 1970 |
| Yellow perch, *Perca flavescens* | 96 | 3.06 | static | Macek and McAllister, 1970 |
| Bluegill sunfish, *Lepomis macrochirus* | 24 | 8.50 | static | Cope, 1963 |
| Bluegill sunfish, *Lepomis macrochirus* | 24 | 6.47 | static | McCann and Jasper, 1972 |
| Bluegill sunfish, *Lepomis macrochirus* | 48 | 8.0 | static | NTACWQC, 1968 |
| Bluegill sunfish *Lepomis macrochirus* | 96 | 4.38 | static | Johnson and Finley, 1980 |
| Bluegill sunfish, *Lepomis macrochirus* | 96 | 2.4 | static | Pickering et al., 1962 |
| Bluegill sunfish, *Lepomis macrochirus* | 96 | 1.9 | static | Weiss, 1964 |

TABLE 6-1 (cont.)

| Species | Duration (hours) | $LC_{50}$ (mg/ℓ) | Method | Reference |
|---|---|---|---|---|
| Bluegill sunfish, Lepomis macrochirus | 40 | 0.115 | static | Hazeltine, 1963 |
| Bluegill sunfish, Lepomis macrochirus | 96 | 5.72 | static | Macek and McAllister, 1970 |
| Largemouth bass, Micupterus salmoides | 96 | 5.22 | static | Macek and McAllister, 1970 |
| Green sunfish, Lepomis cyanellus | 96 | 6.86 | static | Johnson and Finley, 1980 |
| Redear sunfish, Lepomis microlophus | 96 | 5.17 | static | Macek and McAllister, 1970 |
| Channel catfish, Ictalurus punctatus | 96 | 5.24 | static | Johnson and Finley, 1980 |
| Channel catfish, Ictalurus punctatus | 96 | 5.71 | static | Macek and McAllister, 1970 |
| Black bullhead, Ictalurus melas | 96 | 6.64 | static | Macek and McAllister, 1970 |
| Carp, Cyprinus carpio | 48 | 2.0 | static | Spehar et al., 1982 |
| Carp, Cyprinus carpio | 96 | 7.13 | static | Macek and McAllister, 1970 |
| Fathead Minow, Pimephales promelas | 96 | 8.90 | static | Macek and McAllister, 1970 |
| Fathead Minnow, Pimephales promelas | 96 | 0.4 | static | Henderson and Pickering, 1958 |
| Fathead Minnow, Pimephales promelas | 96 | 7.5 | static | Henderson et al., 1959 |
| Fathead minnow, Pimephales promelas | 96 | 9.50 | static | Pickering et al., 1962 |
| Fathead minnow, Pimephales promelas | 96 | 5.36 | flow-through | Jarvinen and Tanner, 1982 |

TABLE 6-1 (cont.)

| Species | Duration (hours) | $LC_{50}$ (mg/ℓ) | Method | Reference |
|---|---|---|---|---|
| Goldfish, Carassius auratus | 96 | 9.00 | static | Macek and McAllister, 1970 |
| Goldfish, Carassius auratus | 96 | 2.0 | static | Pickering et al., 1962 |
| Mosquito fish, Gambusia affinis | 48 | 3.48 | static | Chambers and Yarbrough, 1974 |

and Yarbrough (1974) suggested that mosquito fish exposed to pesticides in nature were less sensitive than fish raised with no previous exposure, suggesting induction of detoxification pathways.

Freshwater invertebrates appear to be more sensitive to methyl parathion than fish. Muncy and Oliver (1963) reported that the 24-, 48- and 72-hour $LC_{50}$ values were 0.05, 0.04 and 0.04 mg/ℓ in crayfish, Procambarus clarkii, with males and females being equally sensitive. In other studies with this crustacean species, Hendrick and Everett (1965) and Hendrick et al. (1966) reported that the median lethal level for 5 days of exposure was <1.0 µg/ℓ, but at the suggested application rate of 25 lb/acre, no toxicity was observed in field studies. Cheah et al. (1980) reported that 96-hour $LC_{50}$ for P. clarkii was 0.003 mg/ℓ. In the crayfish, Orconectes nais, a 96-hour $LC_{50}$ of 0.015 mg/ℓ was reported (Johnson and Finley, 1980). In the crustacean scud, Gammarus fasciatus, the 96-hour $LC_{50}$ was 0.0038 mg/ℓ. In two daphnids, Daphnia magna and Simocephalus serrulatus, 48-hour $LC_{50}$ values were 0.00014 and 0.00037 mg/ℓ, respectively. The $LC_{50}$ values for the aquatic larval stages of the damselfly and gnat were 0.033 (Johnson and Finley, 1980) and 0.0012 (for first instar) (Hazeltine, 1963). In the field, gnats were controlled by methyl parathion at 2.3-3.3 ppb (0.0023-0.0033 mg/ℓ).

The toxicity of methyl parathion has been determined in a number of marine fish and invertebrates (Table 6-2). Of the seven fish species tested by Eisler (1970a), two (Atlantic silverside, striped mullet) had 96-hour $LC_{50}$ values near 5 mg/ℓ, which is close to the sensitivity range of the freshwater fish. Bluehead, striped killifish and American eel were slightly more resistant, with 96-hour $LC_{50}$ values of 12.3, 13.8 and 16.9 mg/ℓ, respectively. The Northern puffer and the mummichog were notably more

TABLE 6-2

Acute Lethal Effects of Methyl Parathion to Marine Organisms

| Species | Duration (hours) | $LC_{50}$ (mg/ℓ) | Method | Reference |
|---|---|---|---|---|
| Striped bass, *Morone saxatilis* | 96 | 0.790 | intermittent-flow | Korn and Earnest, 1974 |
| Atlantic silverside, *Menidia menidia* | 24 | 24.8 | static; aerated | Eisler, 1970a |
| | 48 | 21.9 | static; aerated | |
| | 96 | 5.7 | static; aerated | |
| Bluehead, *Thalassoma bifasciatum* | 24 | 98.0 | static; aerated | Eisler, 1970a |
| | 48 | 88.0 | static; aerated | |
| | 96 | 12.3 | static; aerated | |
| Striped killifish, *Fundulus majalis* | 24 | 29.0 | static; aerated | Eisler, 1970a |
| | 48 | 19.4 | static; aerated | |
| | 96 | 13.8 | static; aerated | |
| Striped mullet, *Mugil cephalus* | 24 | 39.0 | static; aerated | Eisler, 1970a |
| | 48 | 26.3 | static; aerated | |
| | 96 | 5.2 | | |
| American eel, *Anguilla rostrata* | 24 | 27.6 | static; aerated | Eisler, 1970a |
| | 48 | 22.4 | static; aerated | |
| | 96 | 16.9 | static; aerated | |
| Mummichog, *Fundulus heteroclitus* | 24 | >85.2 | static; aerated | Eisler, 1970a |
| | 48 | 85.2 | static; aerated | |
| | 96 | 58.0 | | |
| Northern puffer, *Sphaeraides maculatus* | 24 | 100.0 | static; aerated | Eisler, 1970a |
| | 48 | 91.0 | static; aerated | |
| | 96 | 75.8 | | |
| Mummichog, *Fundulus heteroclitus* | 240 | 0.96 | static; aerated | Eisler, 1970b |
| Pink shrimp, *Penaeus duorarum* | 96 | 0.00120 | flowthrough | Schimmel et al., 1983 |
| Pink shrimp, *Penaeus duorarum* | 96 | 0.0019 | flowthrough | Schoor and Brausch, 1980 |
| Mysid shrimp, *Mysidopsis bahia* | 96 | 0.00078 | flowthrough | Schimmel et al., 1983 |

TABLE 6-2 (cont.)

| Species | Duration (hours) | $LC_{50}$ (mg/ℓ) | Method | Reference |
|---|---|---|---|---|
| Mysid shrimp, *Mysidopsis bahia* | 96 | 0.00077 | intermittent-flow | Nimmo et al., 1981 |
| Sand shrimp, *Crangon septenspinosa* | 96 | 0.002 | static | Eisler, 1969 |
| Gross shrimp, *Palaemonetes vulgoris* | 96 | 0.003 | static | Eisler, 1969 |
| Hermit crab, *Pagurus longicarpus* | 96 | 0.007 | static | Eisler, 1969 |
| Brown shrimp, *Penaeus aztecus* | 24<br>48 | 0.0055<br>0.0055 | static<br>static | Butler, 1963 |

tolerant of methyl parathion, with 96-hour $LC_{50}$ values of 75.8 and 58.0 mg/ℓ, respectively (Eisler, 1970a).

Tests of methyl parathion in the mummichog, Fundulus heteroclitus, were conducted at various salinities and temperatures to determine corresponding toxicity levels (Eisler, 1970b). There was a direct association between temperature and the lethal level, and between salinity and $LC_{50}$ values. Methyl parathion was most toxic to this species at high temperatures and high salinity.

Marine crustaceans appear quite sensitive to methyl parathion (see Table 6-2). Median lethal levels for 96 hours of exposure in five species of shrimp and the hermit crab ranged from 0.007-0.00077 mg/ℓ (7.0-0.77 ppb). Acetylcholinesterase activity of the ventral nerve cord of pink shrimp was inhibited in moribund shrimp exposed to 0.0013 mg methyl parathion/ℓ (1.3 ppb) for 6 hours (Schoor and Brausch, 1980). Animals not moribund showed slightly depressed cholinesterase activity from 6-32 hours of exposure at the same concentration. The MSS as a measure of stamina was reduced in mysid shrimp exposed at $\geq$0.00031-0.00056 mg methyl parathion/ℓ (Cripe et al., 1981).

## 6.2. CHRONIC EFFECTS

Embryo-larval toxicity tests of methyl parathion were conducted in fathead minnows over a 32-day exposure period (Jarvinen and Tanner, 1982). Fifty eggs were exposed to the toxicant and allowed to hatch, and 30 of the healthiest larvae were exposed in chambers for the remainder of the study. Methyl parathion concentrations tested were 0.31, 0.38, 0.59, 0.86 and 1.55 mg/ℓ, and all embryos developed and hatched at these levels. Survival of larvae was 100% in groups exposed at 0.38, 0.31 and 0.00 mg/ℓ. Survival among larvae exposed at 1.55, 0.86 and 0.59 mg/ℓ was 0 (0/30), 30 (9/30)

and 93% (28/30), respectively. Weight gain and growth were significantly decreased in embryo-larval stages exposed at ≥0.38 mg methyl parathion/ℓ. The chronic no-effect concentration for these tests (in Pimephales promelas) was regarded as being between 0.31 and 0.38 mg methyl parathion/ℓ (Jarvinen and Tanner, 1982).

In an abstract of a Russian study, Kokoza and Luk'yanenko (1980) reported that fry and larval stage starred sturgeon were significantly affected at 16.6 and 23.3 mg methyl parathion/ℓ. Growth rate was reduced in both stages, but more so in larvae than in fry. In another Russian study (Guseva, 1980), carp exposed chronically to methyl parathion (exposure level not specified) had reduced fertility and abnormal embryonic development.

In tadpoles of the Pacific tree frog, Hyla regilla, methyl parathion at 0.10 mg/ℓ (100 ppb) for 24 hours significantly lowered thermal tolerance and depressed activity (Johnson, 1980). These effects were noted at exposure levels equal to or less than recommended application rates for mosquito control.

Entire life cycle tests (28 days duration) were conducted in mysid shrimp, M. bahia, to determine a MATC (Nimmo et al., 1981). Survival and reproduction was affected by methyl parathion at levels ≥0.00016 mg/ℓ (0.16 ppb). No significant effect on mortality or the number of young per female was noted at 0.00011 mg methyl parathion/ℓ. The MATC was, therefore, between these values (Nimmo et al., 1981).

## 6.3. PLANT EFFECTS

The green alga, Chlorella protothecoides, was exposed to methyl parathion at 0, 10, 20, 30 and 40 mg/ℓ for 19 days (Saroja and Bose, 1982). Growth of the cultures was monitored by cell counts, packed cell volume and pigment content. Cell numbers were decreased in all exposed cultures

compared to controls, but most notably at 30 and 40 mg/ℓ. At these higher concentrations, cell numbers actually decreased from the initial population and did not recover during the 19-day study. Determinations of packed cell volume and chlorophyll content substantiated the decreased algal growth. All parameters showed a dose-related response on algal growth to methyl parathion concentration (Saroja and Bose, 1982).

Cultures of the marine alga, Sheletonema costatum, were exposed to methyl parathion at 0.0, 2.0, 3.0, 4.0, 5.0 and 6.0 mg/ℓ for 96 hours to determine the concentration causing a 50% decrease in chlorophyll absorbance ($EC_{50}$) at 525 nm (Walsh and Alexander, 1980). A dose-related decrease in growth was reported, with the $EC_{50}$ at 5.3 mg/ℓ.

6.4. RESIDUES

The half-life of methyl parathion in Lake Superior water was 18 days, with >90% degraded within 43 days (Jarvinen and Tanner, 1982). Leard et al. (1980) reported that methyl parathion residues in the Steele Bayou, MS, were 0.25 ppb (µg/ℓ), but none was reported in clam tissue samples taken from the area.

In an abstract of a Russian study (Chigareva, 1973), levels of methyl parathion in the lipid, liver, muscles, gills and brain of carp were 64, 4.4, 1.1, 1.1 and 3.3 mg/kg, respectively. The fish were exposed at 1 mg methyl parathion/ℓ for 2 days. The concentration in body lipid was, therefore, ~70 times the concentration in water.

6.5. OTHER RELEVANT INFORMATION

Jones and Hood (1980) reported that the degradation product of methyl parathion inhibited the ability of estuarine microorganisms to oxidize ammonium compounds. Levels as low as 0.01 mg/ℓ of the methyl parathion

degradation product over a 14-day period caused decreased ammonium oxidation. The parent compound, apparently, did not inhibit ammonium oxidation by the sedimentary populations. This effect may be important in nutrient-nitrogen recycling and nitrification processes (Jones and Hood, 1980).

## 7. EXISTING GUIDELINES AND STANDARDS

### 7.1. HUMAN

A temporary ADI of methyl parathion by humans of 0-0.001 mg/kg was established in December, 1979, at the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (FAO, 1980). The derivation of the ADI was based on a study in humans in which doses of methyl parathion of 7-9 mg/day for 30 days were assessed for cholinesterase inhibition (Moeller and Rider, 1963). FAO (1980) used a no-effect level of 0.1 mg/kg/day and an uncertainty factor of 100. In subsequent studies by these investigators, however, the no-effect level for plasma and RBC cholinesterase inhibition in humans was found to be ~28 mg/day or 0.4 mg/kg/day for a 70 kg human (Rider et al., 1971).

Tolerances for residues of methyl parathion were recommended as 1 mg/kg on vegetables, 0.2 mg/kg on cole crops, Cucurbitaceae and fruit, and 0.05 mg/kg in processed cottonseed oil at the Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues in 1975 (WHO, 1976). The U.S. EPA has established tolerances for residues of methyl parathion in or on raw agricultural commodities at 0.1-5 ppm for grains, hays, fodders, forages, grasses, seeds, fruits, vegetables, beans and nuts, and an interim tolerance in or on rye at 0.5 mg/kg. (Code of Federal Regulations, 198Ca,b).

Both NIOSH (1976) and the ACGIH (1983) have recommended a TWA-TLV for methyl parathion in the workplace environment of 0.2 mg/m$^3$. The TLV was derived based upon the lower toxicity of methyl parathion than parathion to humans in the experiments of Rider et al. (1969) (NIOSH, 1976; ACGIH, 1980).

## 7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of methyl parathion were not located in the available literature.

## 8. RISK ASSESSMENT

Methyl parathion has been tested for carcinogenicity in rats and mice in an NCI (1979) bioassay with negative results. The results of mutagenicity and genotoxicity studies in prokaryotic and eukaryotic systems were equivocal (see Tables 5-1 and 5-2).

The effects of methyl parathion on rat and mice dams and fetuses following treatment of the pregnant animals with the pesticide have been studied by a number of investigators. An oral dose of 3 mg/kg/day on alternate days between 5 and 15 or 5 and 19 of gestation in rats resulted in increased resorptions (Fuchs et al., 1976). No fetal malformations were observed at 3 mg/kg/day, and no treatment-related effects were observed at lower doses. Treatment of pregnant rats with oral doses of methyl parathion of 1.0 or 1.5 mg/kg/day on days 6-15 or 6-19 of gestation resulted in dose-related decreased incorporation of $^{14}$C-valine into protein of maternal and fetal tissue; no other effects were observed (Gupta et al., 1983). Fish (1966) found that i.p. injection of pregnant rats with methyl parathion at 4 or 6 mg/kg on day 9 or 15 of gestation resulted in cholinergic signs and mortality in dams. Fetuses of surviving dams had reduced cerebral cortical cholinesterase activity. No teratogenic or other fetotoxic effects were observed. Methyl parathion at i.p. doses of 5, 10 and 15 mg/kg to pregnant rats or 20 and 60 mg/kg to pregnant mice on day 12 or 10 of gestation, respectively, resulted in signs of cholinergic poisoning, death of dams and reduced body weight and food consumption of surviving dams (Tanimura et al., 1967). High-dose rat fetuses had reduced body weight and delayed ossification of caudal vertebrae compared with controls ($p<0.05$). High-dose mouse fetuses had a significantly increased incidence of cleft palate ($p<0.05$), reduced body weight, increased incidence of cervical rib ($p<0.05$) and delayed ossification of caudal vertebrae ($p<0.05$) compared with controls.

No consistent effects on mortality, weanling body weight, reproductive performance or other parameters were observed in rats at dietary levels of 10 or 30 ppm methyl parathion throughout three generations (Lobdell and Johnston, 1966).

Since methyl parathion has not been shown to be carcinogenic, it is appropriate to derive an ADI from toxicity data. The only available study of long-term duration is the NCI (1979) bioassay. Rats receiving methyl parathion at 20 and 40 ppm in the diet had dose-related decreased mean body weight, and high-dose females had increased mortality. Mice receiving dietary levels of methyl parathion at TWA concentrations of 35 and 77 ppm had decreased body weight in high-dose males. It is not appropriate to derive an ADI for methyl parathion based upon the reduced body weight data in the NCI (1979) study because data on food consumption and the statistical significance of the difference in body weights were not reported. Furthermore, in the absence of other clinical or histological signs, it is not possible to assess the toxicologic significance of reduced body weight. Rabbits receiving dietary levels of methyl parathion of 0.6, 2.6, 8.5 and 23 ppm for 8 weeks and challenged with antigen at 4 weeks had reduced numbers of plasma cells that produced gamma-globulin, reduced germinal center counts of spleen and atrophy of thymus cortex (Street and Sharma, 1975). In the absence of any immunosuppressive or other toxic effects, the toxicological significance of these findings is difficult to assess. In a 90-day feeding study in dogs, Williams et al. (1959) found that a dietary level of methyl parathion of 5 ppm was a no-effect level for RBC and plasma cholinesterase inhibition. At 20 and 50 ppm, the RBC and plasma cholinesterase activities showed dose-related decreases from pretreatment values which were statistically significant. In contrast to the observed recovery of cholinesterase activity

during the treatment of dogs with Dipterex, Chlorthion and Diazinon, maximum inhibition of RBC or plasma cholinesterase was not reached during methyl parathion treatment, indicating a more cumulative effect with methyl parathion. The no-effect dietary level of 5 ppm methyl parathion for 90 days in dogs could be used to derive an ADI for humans; however, data for cholinesterase inhibition in humans are available. In a series of experiments involving five treated and two control men per determination, the minimum effective dose for RBC cholinesterase inhibition was established (Moeller and Rider, 1959, 1961, 1962, 1963; Rider and Moeller, 1964; Rider et al., 1966, 1967, 1969, 1970, 1971). In the first experiment, 1 mg methyl parathion/day for ~30 days was ingested. In subsequent determinations, the dose was gradually increased in increments of 0.5 mg/day. Only at $\geq$24 mg/day were significant reductions in individual cholinesterase activities observed. At 28 mg/day (0.4 mg/kg/day for a 70 kg human), the mean maximum inhibition of RBC cholinesterase was 19%; at 30 mg/day, (0.43 mg/kg/day for a 70 kg human), the mean maximum inhibition of RBC cholinesterase was 37%. Since no clinical signs or effects on urinalysis and hematologic parameters were observed, 30 mg/day represents a LOEL, while 28 mg/day is the human NOEL for RBC cholinesterase inhibition. In general, RBC cholinesterase inhibition is not considered an adverse effect; the inhibition of brain cholinesterase has more functional significance (Wills, 1972). However, RBC cholinesterase is chemically similar to brain cholinesterase, the inhibition of which has been demonstrated in acute studies of rats (Toth et al., 1980; Yamamoto et al., 1982) and mice (Benke and Murphy, 1974) at high doses.

A dose of 1.3 mg/kg/day orally for 10 days resulted in significant inhibition (~56% of control; $p<0.05$) of brain cholinesterase activity in rats (Yamamoto et al., 1982). The dose of 1.3 mg/kg/day in rats is only

3-fold greater than the LOEL for RBC inhibition in humans (0.43 mg/kg/day) (Rider et al., 1971). Therefore, inhibition of RBC cholinesterase may be indicative of inhibition of brain cholinesterase. With prolonged exposure to anticholinesterase agents, the inhibition of cholinesterase generally becomes no worse than with shorter term exposure, although, as demonstrated in dogs, maximum cholinesterase inhibition by methyl parathion had not been reached during the 90-day feeding study (Williams et al., 1959). It is, therefore, appropriate to use an uncertainty factor of 100 for a subchronic human NOEL to protect the most sensitive individual.

The ADI can be calculated as:

$$\text{ADI} = \frac{28 \text{ mg/day}}{100}$$

$$= 0.28 \text{ mg/day}$$

Assuming that an average human weighs 70 kg, this ADI is equivalent to 0.004 mg/kg/day.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance.

## 9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983.) Cincinnati, OH. p. 285-286.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment with Intended Changes for 1983-1984. Cincinnati, OH. p. 26.

Ackermann, H. and R. Engst. 1970. Presence of organophoshate insecticides in the fetus. Arch. Toxkol. 26: 17-22. (Ger.) (Cited in NIOSH, 1976)

Adhya, T.K., B. Sudhakar-Barik and N. Sethunathan. 1981. Fate of fenitrothion, methyl parathion, and parathion in anoxic sulfur-containing soil system. Pest. Biochem. Phys. 16: 14-20.

Akhmedov, B.K. and V.B. Danilov. 1969. Morphological, pathological and histochemical changes in the organs of rats during long term exposure to metaphos and carbophos vapors. Med. Zh. Uzb. 3: 17-18. (Rus.) (Cited in NIOSH, 1976)

Arthur, R.D., J.D. Cain and B.F. Barrentine. 1976. Atmospheric levels of pesticides in the Mississippi Delta. Bull. Environ. Contam. 15(2): 129-134.

Baker, R.D. and H.G. Applegate. 1970. Effect of temperature and ultraviolet radiation on the persistence of methyl parathion and DDT in soil. Agron. J. 62: 509-512.

Baker, R.D. and H.G. Applegate. 1974. Effect of ultraviolet radiation on the persistence of pesticides. Toxicol. J. Sci. 25: 53-59.

Barnes, J.M. and F.A. Denz. 1953. Experimental demyelination with organophosphorus compounds. J. Pathol. Bacteriol. 65: 597-605.

Baughman, G.L. and R.R. Lassiter. 1978. Prediction of environmental pollutant concentration. In: Estimating the Hazard of Chemical Substances to Aquatic Life, J. Cairns, Jr., K.L. Dickson and A.W. Maxi, Ed. American Society for Testing and Materials, Philadelphia, PA. p. 35-54. ASTM STP657.

Benke, G.M. and S.D. Murphy. 1974. Antichloinesterase action of methyl parathion, parathion, and azinphosmethyl in mice and fish. Onset and recovery of inhibition. Bull. Environ. Contam. Toxicol. 12(1): 117-122.

Benke, G.M. and S.D. Murphy. 1975. Influence of age on the toxicity and metabolism of methyl parathion and parathion in male and female rats. Toxicol. Appl. Pharmacol. 31(2): 254-269.

Benke, G.M., K.L. Cheever, F.E. Mirer and S.D. Murphy. 1974. Comparative toxicity, anticholinesterase action, and metabolism of methyl parathion and parathion in sunfish and mice. Toxicol. Appl. Pharmacol. 28(1): 97-109.

Braeckman, R.A., M.G. Godefroot, G.M. Blondeel, F.M. Belpaire and J.L. Willems. 1980. Kinetic analysis of the fate of methyl parathion in the dog. Arch. Toxicol. 43(4): 263-271.

Braeckman, R.A., F. Audenaert, J.O. Willems, F.M. Belpaire and M.G. Bogaert. 1983. Toxicokinetics of methyl parathion in the dog after intravenous and oral administration. Arch. Toxicol. 54(1): 71-82.

Burns, L.A., D.M. Cline and R.R. Lassiter. 1982. Exposure Analysis Modeling System (EXAMS): User Manual and System Documentation. Environmental Research Laboratory, U.S. EPA, Office of Research and Development, Athens, GA. EPA 600/3-82-023.

Butler, L.C., D.C. Stauff and J.E. Davis. 1981. Methyl parathion persistence in soil following simulated spillage. Arch. Environ. Contam. Toxicol. 10: 451-458.

Butler, P.A. 1963. Commercial Fishery Investigations. In: Pesticide-Wildlife Studies, 1963. A Review of Fish and Wildlife Service Investigations During the Calendar Year. Fish and Wildl. Serv., Circular 199. USDI, Washington, DC.

Butler, P.A. and R.L. Schutzmann. 1978. Residues of pesticides and PCBs in estuarine fish, 1972-1976. National Pesticide Monitoring Program. Pest. Monitor. J. 12: 51-59.

Cabejszek, I., S. Szulinski. 1966. Effect of methylparathion in drinking water on warm blooded animals. Rocz. Panstw. Zakl. Hig. 17(5): 491-498. (Pol.) (CA 66: 1145765g)

Carere, A., V.A. Ortali, G. Cardamone and G. Morpurgo. 1978. Mutagenicity of dichlorvos and other structurally related pesticides in Salmonella and Streptomyces. Chem. Biol. Interact. 22(2-3): 297-308.

Carricaburu, P., R. Lacroix and J. Lacroix. 1980. Electroretinographic study of the white mouse intoxication by organophosphorus: Methyl parathion, parathion and paraoxon. Pestic. Biochem. Physiol. 13(3): 244-248.

Chambers, J.E. and J.D. Yarbrough. 1974. Parathion and methyl parathion toxicity to insecticide-resistant and susceptible mosquitofish (Gambusia affinis). Environ. Contam. Toxicol. 11(4): 315-320.

Cheah, M.L., J.W. Avault and J.B. Graves. 1980. Acute toxicity of selected rice pesticides to crayfish Procambarus clarkii. Prog. Fish Cult. 42(3): 169-172.

Chen, H.H., J.L. Hsueh, S.R. Sirianni and C.C. Huang. 1981. Induction of sister-chromatid exchanges and cell cycle delay in cultured mammalian cells treated with eight organophosphorus pesticides. Mutat. Res. 88(3): 307-316.

Chen, H.H., S.R. Sirianni and C.C. Huang. 1982. Sister chromatid exchanges in Chinese hamster cells treated with seventeen organophosphorus compounds in the presence of a metabolic activation system. Environ. Mutagen. 4(5): 621-624.

Chigareva, O.I. 1973. Metaphos distribution in fish organs and tissues. Tr., Vses. Nauchno-Issled Inst. Vet. Sanit. 46: 102-104. (Rus.) (CA 84: 1015)

Code of Federal Regulations. 1980a. Parathion or its Methyl Homolog; Tolerances for Residues. 40 CFR 80.121.

Code of Federal Regulations. 1980b. Interim Tolerances. 40 CFR 180.319.

Cope, O.B. 1963. Sport Fisheries Investigations. U.S. Fish and Wildl. Serv. Circular No. 167. USDI, Washington, DC. p. 26-42.

Cripe, G.M., D.R. Nimmo and T.L. Hamaker. 1981. Effects of two organophosphate pesticides on swimming stamina of the mysid Mysidopsis bahia. Biol. Monit. Mar. Pollut. p. 21-36. (CA 95: 75044)

Crossland, N.O. and K.E. Elgar. 1983. Fate and biological effects of insecticides in ponds. Pestic. Chem. 3: 551-556.

Crowder, L.A., G.C. Lanzaro and R.S. Whitson. 1980. Behavioral effects of methyl parathion and toxaphene exposure in rats. J. Environ. Sci. Health B. 15(4): 365-378.

Chen, H.H., S.R. Sirianni and C.C. Huang. 1982. Sister chromatid exchanges in Chinese hamster cells treated with seventeen organophosphorus compounds in the presence of a metabolic activation system. Environ. Mutagen. 4(5): 621-624.

Chigareva, O.I. 1973. Metaphos distribution in fish organs and tissues. Tr., Vses. Nauchno-Issled Inst. Vet. Sanit. 46: 102-104. (Rus.) (CA 84: 1015)

Code of Federal Regulations. 1980a. Parathion or its Methyl Homolog; Tolerances for Residues. 40 CFR 80.121.

Code of Federal Regulations. 1980b. Interim Tolerances. 40 CFR 180.319.

Cope, O.B. 1963. Sport Fisheries Investigations. U.S. Fish and Wildl. Serv. Circular No. 167. USDI, Washington, DC. p. 26-42.

Cripe, G.M., D.R. Nimmo and T.L. Hamaker. 1981. Effects of two organophosphate pesticides on swimming stamina of the mysid Mysidopsis bahia. Biol. Monit. Mar. Pollut. p. 21-36. (CA 95: 75044)

Crossland, N.O. and K.E. Elgar. 1983. Fate and biological effects of insecticides in ponds. Pestic. Chem. 3: 551-556.

Crowder, L.A., G.C. Lanzaro and R.S. Whitson. 1980. Behavioral effects of methyl parathion and toxaphene exposure in rats. J. Environ. Sci. Health B. 15(4): 365-378.

Davidson, J.M., P.S.C. Rao, L.T. Ou, W.B. Wheeler and D.F. Rothwell. 1980. Adsorption, movement and biological degradation of large concentrations of pesticides in soils. U.S. EPA, Cincinnati, OH. EPA 600/2-80-124. 124 p.

Dean, B.J. 1972. The mutagenic effects of organophosphorus pesticides on microorganisms. Arch. Toxikol. 30: 67-74. (CA 78: 119675z)

De Cassia, S.R., W. Becak, R. Gaeta and M.M. Rabellogay. 1982. Cytogenetic study of workers exposed to methyl-parathion. Mutat. Res. 103(1): 71-76.

Degraeve, N., J. Moutschen, M. Moutschen-Dahmen, et al. 1979. Genetic effects of organophosphate insecticides in mouse. Mutat. Res. 64(2): 131.

Degraeve, N., M.C. Chollet, J. Moutschen, M. Moutschen-Dahmen, J. Gilot-Delhalle and A. Colizzi. 1982. Genetic and cytogenetic effects of chronic treatments with organophosphorus insecticides. Mutat. Res. 97: 179-180.

Eichelberger, J.W. and J.J. Lichtenberg. 1971. Persistence of pesticides in river water. Environ. Sci. Technol. 5: 541-544.

Eisler, R. 1969. Acute toxicities of insecticides to marine decapod crustacean. Crustaceana. 16(3): 302-310.

Eisler, R. 1970a. Acute toxicities of organochlorine and organophosphorus insecticides to estuarine fishes. Tech. Pap. Bur. Sport Fish. Wildl. No. 45-46. 12 p.

Eisler, R. 1970b. Factors affecting pesticide-induced toxicity in an estuarine fish. Tech. Pap. Bur. Sport Fish. Wildl. No. 45-46. 20 p.

Enan, E.E., O.H. Enan and A.E. El-Sebae. 1982. Biochemical targets affected by sublethal doses of organophosphorus insecticides. Int. Pest. Control. 24(5): 120-122. (CA 98: 84594f, 1983)

Ercegovich, C.D. and K.A. Rashid. 1977. Mutagenesis induced in mutant strains of Salmonella typhimurium by pesticides. Am. Chem. Soc. Abstr. Pap. 174: 43.

Fahrig, R. 1974. Comparative mutagenicity studies with pesticides. IARC Sci. Publ. 10: 161-181.

FAO (Food and Agricultural Organization). 1980. Pesticide Residues in Food: 1979. Evaluations, Rome. p. 367-368. (Cited in IARC, 1983)

Fish, S.A. 1966. Organophosphorus cholinesterase inhibitors and fetal development. Am. J. Obstet. Gynecol. 96(8): 1148-1154.

Fuchs, V., S. Golbs, M. Kuehnert and F. Osswald. 1976. Studies of prenatal toxicity of parathion-methyl on Wistar rats and comparison with prenatal toxicity of cyclophosphamide and trypan blue. Arch. Exp. Veterinaermed. 30: 343-350. (CA 86: 8192, 1977)

Fukami, J. and T. Shishido. 1966. Nature of a soluble, glutathione-dependent enzyme system active in cleavage of methyl parathion to demethyl parathion. J. Econ. Entomol. 59(8): 1338-1346.

Gaines, T.B. 1969. Acute toxicity of pesticides. Toxicol. Appl. Pharmacol. 14(3): 515-534.

Galal, E.E., L.M. Abdel, M. Kandil and S. Kamel. 1975. The percutaneous cardiac toxicokinesis of anticholinesterase insecticides. J. Drug Res. 7(2): 29-43.

Galal, E.E., H.A. Samaan and S. Nour El Din. 1977. Studies on the acute and subchronic toxicities of some commonly used anticholinesterase insecticides in rats. J. Drug Res. 9(1-2): 1-17. (CA 89: 192099w, 1978)

Gile, J.D. and J.W. Gilbert. 1981. Transport and fate of organophosphate insecticides in a laboratory model ecosystem. J. Agric. Food Chem. 29(3): 616-621.

Gilot-Delhalle, J., A. Colizzi, J. Moutschen and M. Moutschen-Dahmen. 1983. Mutagenicity of some organophosphorus compounds at the ade6 locus of Schizosaccharomyces pombe. Mutat. Res. 117(1-2): 139-148.

Griffin, D.E., III and W.E. Hill. 1978. In vitro breakage of plasmid DNA by mutagens and pesticides. Mutat. Res. 52(2): 161-169.

Gupta, R.C., F. Welsch and J.E. Thornburg. 1983. Inhibition of Protein-Synthesis in Pregnant Rats and Their Fetuses After Prenatal Exposure to Methylparathion. Fed. Proc., Michigan State Univ., Lansing, MI.

Guseva, S.S. 1980. Gonadotropic action of metaphos on carp. Deposited Doc. (Rus.) 23 p. (CA 96: 47267)

Hansch, C. and A.J. Leo. 1981. Medchem Project. Issue No. 19. Pomona College, Claremont, CA.

Hazeltine, W.E. 1963. The development of a new concept for control of the Clear Lake gnat. J. Econ. Entomol. 56: 621-626.

Henderson, C. and Q.H. Pickering. 1958. Toxicity of organic phosphorus insecticides to fish. Trans. Am. Fish. Soc. 87: 39-51.

Henderson, C., Q.H. Pickering and C.M. Tarzwell. 1959. Relative toxicity of ten chlorinated hydrocarbon insecticides to four species of fish. Trans. Amer. Fish. Soc. 88(1): 23-32.

Hendrick, R.D. and T.R. Everett. 1965. Toxicity to Louisiana red crawfish of some pesticides used in rice culture. J. Econ. Entomol. 58: 958-961.

Hendrick, R.D., T.R. Everett and H.R. Coffey. 1966. Effects of some insecticides on the survival, reproduction and growth of the Louisiana red crawfish. J. Econ. Entomol. 59: 188-192.

Hirschelmann, R. and H. Bekemeier. 1975. Acute toxicity of demephion and parathion methyl in dogs. Proc. Eur. Soc. Toxicol. 16: 273-257.

Hollingworth, R.M., R.L. Metcalf and T.R. Fukuto. 1967. Selectivity of Sumithion compared with methyl parathion. Metabolism in the white mouse. J. Agric. Food Chem. 15(2): 242-249.

Huang, C.C. 1973. Effect of growth but not on chromosomes of the mammalian cells after treatment with three organophosphorus insecticides. Proc. Soc. Exp. Biol Med. 142(1): 36-40.

IARC (International Agency for Research on Cancer). 1983. Methyl parathion. In: Miscellaneous Pesticides. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyon, France. Vol. 30, p. 131-152.

Jackson, M.D. and R.G. Lewis. 1978. Volatilization of two methyl parathion formulations from treated fields. Bull. Environ. Contam. Toxicol. 20(6): 793-796.

Jarvinen, A.W. and D.K. Tanner. 1982. Toxicity of selected controlled release and corresponding unformulated technical grade pesticides to the fathead minnow Pimephales promelas. Environ Pollut. Ser. A. Ecol. Biol. 27(3): 179-196.

Johnsen, R.E. and P.A. Dahm. 1966. Activation and degradation efficiencies of liver microsomes from eight vertebrate species, using organophosphates as substrates. J. Econ. Entomol. 59(6): 1437-1442.

Johnson, C.R. 1980. Effects of 5 organophosphorus insecticides on thermal stress in tadpoles of the Pacific tree frog, Hyla regilla? Zool. J. Linn. Soc. 69(2): 143-148.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Fish and Wildl. Serv. Res., Pub. No. 137. USDI, Washington, DC.

Jones, R.D. and M.A. Hood. 1980. The effects of organophosphorus pesticides on estuarine ammonium oxidizers. Can. J. Microbiol. 26(11): 1296-1299.

Jorgenson, T.A., C.J. Rushbrook and G.W. Newell. 1976. In vivo mutagenesis investigations of ten commercial pesticides. Toxicol. Appl. Pharmacol. 37: 109.

Kenaga, E.E. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol. Environ. Safety. 4: 26-38.

Kokoza, A.A. and V.I. Luk'yanenko. 1980. Age dynamics of the resistance of starred sturgeon in early ontogenesis to pesticides. Rybn. Khoz. (Rus.) ISS 6. p. 38. (CA 93: 126705)

Korn, S. and R. Earnest. 1974. Acute toxicity of twenty insecticides to striped bass, Morone saxatilis. Calif. Fish Game. 60(3): 128-131.

LaBel, G.L., D.T. Williams, G. Griffith and F.M. Benoit. 1979. Isolation and concentration of organophosphorus pesticides from drinking water at the ng/ℓ level, macroreticular resin. J. Assoc. Off. Anal. Chem. 62(2): 241-249.

Leard, R.L., B.J. Grantham and G.F. Pessoney. 1980. Use of selected freshwater bivalves for monitoring organochlorine pesticide residues in major Mississippi stream systems, 1972-1973. Pestic. Monit. J. 14(2): 47-52.

Lee, T.P., R. Moscati and B.H. Park. 1979. Effects of pesticides on human leukocyte functions. Res. Commun. Chem. Pathol. Pharmacol. 23(3): 597-609. (CA 91: 148567)

Levine, B.S. and S.D. Murphy. 1977. Effect of piperonyl butoxide on the metabolism of dimethyl and diethyl phosphorothionate insecticides. Toxicol. Appl. Pharmacol. 50(3): 40(3): 393-406.

Lewis, D.L. and H.W. Holm. 1981. Rates of tranformation of methyl parathion and diethyl phthalate by aufwuchs microorganisms. Appl. Environ. Microbiol. 42: 698-703.

Lobdell, B.J. and C.D. Johnston. 1966. Methyl parathion-three-generation reproduction study in the rat. Woodard Research Corp., Herndon, VA. p. 1-64. (Cited in NIOSH, 1976)

Mabey, W. and T. Mill. 1978. Critical review of hydrolysis of organic compounds in water under environmental conditions. J. Phys. Chem. Ref. Data. 7: 383-415.

Mabey, W.R., J.H. Smith, R.T. Podoll, et al. 1981. Aquatic Fate Process Data for Organic Priority Pollutants. U.S. EPA, Monitoring and Data Support Div., Office of Water Regulations and Standards, Washington, DC. EPA 440/4-81-014.

Macek, K.S. and W.A. McAllister. 1970. Insecticide susceptibility of some common fish family representative. Trans. Am. Fish. Soc. 1: 20-27.

McCann, J.A. and R.L. Jasper. 1972. Vertebral damage to bluegills exposed to acutely toxic levels of pesticides. Trans. Am. Fish. Soc. 101(2): 317-322.

Metcalf, R.L., L.K. Cole, S.G. Wood, D.J. Mandel and M.L. Milbrath. 1979. Design and evaluation of a terrestrial model ecosystem for evaluation of substitute pesticide chemicals. Environmental Res. Lab., Corvallis, OR. EPA 600/3-79-004. 308 p.

Metcalfe, C.D., D.W. McLeese and V. Zitko. 1980. Rate of volatilization of fenitrothion from fresh water. Chemosphere. 9(3): 151-155.

Mirer, F.E., B.S. Levine and S.D. Murphy. 1977. Parathion and methyl parathion toxicity and metabolism in piperonyl butoxide and diethyl maleate pretreated mice. Chem.-Biol. Interact. 17(1): 99-112.

Miyamoto, J. 1964. Studies on the mode of action of organophosphorus compounds--Part III. Activation and degradation of sumithion and methylparathion in mammals in vivo. Agric. Biol. Chem. 28: 411-421. (Cited in NIOSH, 1976)

Moeller, H.C. and J.A. Rider. 1959. The effects of various organic phosphate insecticides on RBC and plasma cholinesterase in humans. Fed. Proc. 18: 424.

Moeller, H.C. and J.A. Rider. 1961. Studies on the anticholinesterase effect of parathion and methyl parathion in humans. Fed. Proc. 20: 434.

Moeller, H.C. and J.A. Rider. 1962. Threshold of incipient toxicity to Systox and methyl parathion. Fed. Proc. 21: 451.

Moeller, H.C. and J.A. Rider. 1963. Further studies on the toxicity of Systox and methyl parathion. Fed. Proc. 22: 189.

Molozhanova, E.G. 1980. Distribution dynamics of organophosphate pesticides in the soil and their migration in the soil-water ecological system. Migr. Zagryaz. Veshchestv Pochvakh Sopredel-Nykh Srekakh, Tr. Vses. Soveshch. 2: 232-234.

Morgan, D.P., H.O. Hetzler, E.F. Slach and L.I. Lin. 1977. Urinary excretion of paranitrophenol and alkyl phosphates following ingestion of methyl or ethyl parathion by human subjects. Arch. Environ. Contam. Toxicol. 6(2-3): 159-173.

Muncy, R.J. and A.O. Oliver, Jr. 1963. Toxicity of 10 insecticides to the red crawfish, Procambarus clarkii (Girard). Trans. Am. Fish. Soc. 92: 428-431.

Murphy, S.D. 1980. Toxic interactions with dermal exposure to organophosphate insecticides. Toxicol. Lett. 5(Sp 1): 34.

Murphy, S.D. 1982. Toxicity and hepatic metabolism of organophosphate insecticides in developing rats. Banbury Rep. 11: 125-136.

Nakatsugawa, T., N.M. Tolman and P.A. Dahm. 1968. Degradation and activation of parathion analogs by microsomal enzymes. Biochem. Pharmacol. 17(8): 1517-1528.

NCI (National Cancer Institute). 1979. Bioassay of methyl parathion for possible carcinogenicity. NCI Carcinogenesis Tech. Rep., Ser. No. 1157. 112 p. [DHEW (NIH) 79-1713]

Newell, G.W. and J.V. Dilley. 1978. Teratology and acute toxicity of selected chemical pesticides administered by inhalation. NTIS PB: 277-077.

Nimmo, D.R., T.L. Hamaker, E. Matthews and J.C. Moore. 1981. An overview of the acute and chronic effects of first and second generation pesticides on an estuarine mysid. Biol. Monit. Mar. Pollut. p. 3-19.

NIOSH (National Institute for Occupational Safety and Health). 1976. Criteria for a Recommended Standard...Occupational Exposure to Methyl Parathion. U.S. DHEW, PHS, CDC, Rockville, MD. Publ. No. 77-106.

NIOSH (National Institute for Occupational Safety and Health). 1983. RTECS, May, 1983: Online.

NTACWQC (National Technical Advisory Committee on Water Quality Control). 1968. Water Quality Criteria: Report of the National Technical Advisory Committee to the Secretary of the Interior. USDI, Washington, DC.

Ohkawa, H., H. Oshita and J. Miyamoto. 1980. Comparison of inhibitory activity of various organophosphorus compounds against acetylcholinesterase and neurotoxic esterase of hens with respect to delayed neurotoxicity. Biochem. Pharmacol. 29(20): 2721-2727.

Pevny, I. 1980. Allergy to pesticides. Allergic contact eczema affliction of a vintner. Dermatosen Beruf Umwelt. 28(6): 186-189. (Ger.) (Taken from PESTAB 81/1370)

Pfaender, F., M.S. Shuman, H. Dempsey and C.W. Harden. 1977. Monitoring heavy metals and pesticides in the Cape Fear River Basin of North Carolina. Report 126. Off. Water Res. Technol., Washington, DC. 157 p.

Pickering, Q.H, C. Henderson and A.E. Lemki. 1962. The toxicity of organic phosphorus insecticides to different species of warmwater fishes. Trans. Am. Fish. Soc. 91: 175-184.

Rao, S.L.N. and W.P. McKinley. 1969. Metabolism of organophosphorus insecticides by liver homogenates from different species. Can. J. Biochem. 47(12): 1155-1159.

Reinbold, K.A., J.J. Hassett, J.C. Means and W.L. Banwart. 1979. Adsorption of Energy-Related Organic Pollutants: A Literature Review. U.S. EPA, Athens, GA. EPA 600/3-79-086. 180 p.

Riccio, E., G. Shepherd, A. Pomeroy, K. Mortelmans and M.D. Waters. 1981. Comparative studies between the S. cerevisiae D3 and D7 assays of eleven pesticides. Environ. Mutagen. 3(3): 327.

Rider, J.A. and H.C. Moeller. 1964. Studies on the anticholinesterase effects of Systox and methyl parathion in humans. Fed. Proc. 23: 175. (Cited in NIOSH, 1976)

Rider, J.A., H.C. Moeller and E.J. Puletti. 1966. Continuing studies on anticholinesterase effect of methyl parathion in humans and determination of level of incipient toxicity of OMPA. Fed. Proc. 25: 687. (Cited in NIOSH, 1976)

Rider, J.A., H.C. Moeller and E.J. Puletti. 1967. Continuing studies on anticholinesterase effect of methyl parathion, initial studies with Guthion, and determination of incipient toxicity level of Dichlorvos in human. Fed. Proc. 26: 427. (Cited in NIOSH, 1976)

Rider, J.A., H.C. Moeller, E.J. Puletti and J.I. Swader. 1969. Toxicity of parathion, Systox, octamethylpyrophosphoramide, and methyl parathion. Toxicol. Appl. Pharmacol. 14(3): 603-611.

Rider, J.A., J.I. Swader and E.J. Puletti. 1970. Methyl parathion and guthion anticholinesterase effects in human subjects. Fed. Proc. 29: 349.

Rider, J.A., J.I. Swader and E.J. Puletti. 1971. Anticholinesterase toxicity studies with methyl parathion, guthion and phosdrin in human subjects. Fed. Proc. 30: 443.

Rodnitzky, R.L., H.S. Levin and D.P. Morgan. 1978. Effects of ingested parathion on neurobehavioral functions. Clin. Toxicol. 13(3): 347-359.

Samedov, I.G., I.A. Bekeshev and L.N. Mamedova. 1979. Nonspecific immunological response of animals under the long-term effect of the pesticides polidofen and metaphos. Azerb. Med. Zh. 56(11): 13-17. (Rus.) [CA 92(15)122997a]

Sanborn, J.R., B.M. Francis and R.L. Metcalf. 1977. The degradation of selected pesticides in soil: A review of the published literature. U.S. EPA, Municipal Environmental Research Laboratory, Office of Research and Development, Cincinnati, OH. p. 416-445. EPA 600/9-77-022.

Saroja, G., and S. Bose.. 1982. Effects of methyl parathion on the growth, cell size, pigment and protein content of Chlorella protothecoides. Environ. Pollut. Ser. A. Ecol. Biol. 27(4): 297-308.

Schimmel, S.C., R.L. Garnas, J.M. Patrick, Jr. and J.C. Moore. 1983. Acute toxicity, bioconcentration, and persistence of AC 222,705, benthiocarb, chlopyrifos, fenvalerate, methyl parathion, and permethrin in the estuarine environment. J. Agric. Food Chem. 31(1): 104-113.

Schoor, W.P. and J. Brausch. 1980. The inhibition of acetylcholinesterase activity in pink shrimp (Penaeus duorarum) by methyl parathion and its oxon. Arch. Environ. Contam. Toxicol. 9(5): 599-605.

Skinner, C.S. and W.W. Kilgore. 1982a. Application of a dermal self-exposure model to worker reentry. J. Toxicol. Environ Health. 9(3): 461-482. (CA 97: 86641x)

Skinner, C.S. and W.W. Kilgore. 1982b. Acute dermal toxicities of various organophosphate insecticides in mice. J. Toxicol. Environ. Health. 9(3): 491-498. (CA 97: 34419m)

Smith, J.H., W.R. Mabey, N. Bohonus, et al. 1978. Environmental pathways of selected chemicals in freshwater systems. Part II. Laboratory studies. U.S. EPA, Athens, GA. EPA 600/7-78-074.

Sobti, R.C., A. Krishan and C.D. Pfaffenberger. 1982. Cytokinetic and cytogenetic effects of some agricltural chemicals on human lymphoid cells in vitro: Organophosphates. Mutat. Res. 102(1): 89-102.

Spehar, R.L., G.M. Christensen, C. Curtis, A.E. Lenke, T.J. Norberg and Q.H. Pickering. 1982. Effects of pollution on freshwater fish. J. Water Pollut. Control Fed. 54(6): 877-922.

Spencer, W.F., T.D. Shoup, M.M. Cleath, W.J. Farmer and R. Haque. 1979. Vapor pressure and relative volatility of ethyl and methyl parathion. J. Agric. Food Chem. 27: 273-278.

SRI (Stanford Research Institute). 1983. Directory of Chemical Producers, United States of America. SRI International, Menlo Park, CA. p. 783.

Stanley, C.W., J.E. Barney, II, M.R. Helton and A.R. Yobs. 1971. Measurement of atmospheric levels of pesticides. Environ. Sci. Technol. 5(5): 430-435.

Street, J.C. and R.P. Sharma. 1975. Alterations of induced cellular and humoral immune responses by pesticides and chemicals of environmental concern. Quantitative studies of immunosuppression by DDT, Aroclor 1254, carbaryl, carlufuran, and methylparathion. Toxicol. Appl. Pharmacol. 32: 587-602.

Tanimura, T., T. Katsuya and H. Nishimura. 1967. Embryotoxicity of acute exposure to methyl parathion in rats and mice. Arch. Environ. Health. 15(5): 609-613.

Tessari, J.D. and D.L. Spencer. 1971. Air sampling for pesticides in the human environment. J. Ass. Offic. Anal. Chem. 54(6): 1376-1382.

Toth, L. S. Karscu, G. Marosi and Z. Simon. 1980. Histochemical analysis of the multiple effect of organpohosphorous compounds (Mofatox, DFP) in rats. Acta Histochem. 66(2): 220-235. (Ger.)

Uchiyama, M., T. Yashida, K. Homma and T. Hongo. 1975. Inhibition of hepatic drug-metabolizing enzymes by thiophosphate insecticides and its drug toxicological implications. Biochem. Pharmacol. 24(11-12): 1221-1225.

USITC (United States International Trade Commission). 1983. Synthetic Organic Chemicals: United States Production and Sales, 1982. USITC, Washington, DC. p. 233. USITC Publ. 1422.

Von Rumker, R., E.W. Lawless and A.F. Meiners. 1974. Production, Distribution, Use and Environmental Impact Potential of Selected Pesticides. Final Report under Contract EQC-311 for Council on Environmental Quality, Washington, DC. p. 181-188.

Wade, M.J. 1979. Organophosphorus pesticides in the marine environment: Their transport and fate. Diss. Abst. Int. 40: 4704.

Walker, W.W. 1981. Development of a Fate/Toxicity Screening Test. Final Draft Report under Contract 61-01-5043 for U.S. EPA, Office of Pesticide and Toxic Substances, Washington, DC.

Walsh, G.E. and S. Alexander. 1980. A marine algal bioassay method: Results with pesticides and industrial wastes. Water Air Soil Pollut. 13(1): 45-55.

Ware, G.W., D.P. Morgan, B.J. Estesen, W.P. Cahill and D.M. Whitacre. 1973. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. I. Ethyl- and methyl parathion. Arch. Environ. Contam. Toxicol. 1(1): 48-59.

Ware, G.W., D.P. Morgan, B.J. Estesen and W.P. Cahill. 1974. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. II. Asodrin, ethyl and methyl parathion. Arch. Environ. Contam. Toxicol. 2(2): 117-129.

Ware, G.W., D.P.Morgan, B.J. Estesen and W.P. Cahill. 1975. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. III. 12 to 72 hours post-treatment exposure to monocrotophos, ethyl- and methyl parathion. Arch. Environ. Contam. Toxicol. 3(3): 289-306.

Waters, M.D., S.S. Shanhu, V.F. and V.F. Simmon. 1982. Study of pesticide genotoxicity. Basic Life Sci. 21: 275-326.

Wauchope, R.D. and R.A. Leonard. 1980. Maximum pesticide concentrations in agricultural runoff: A semiempirical prediction formula. J. Environ. Qual. 9: 665-672.

Weisburger, E.K. 1982. Carcinogenicity tests on pesticides. Eff. Chronic Exposures Pestic. Anim. Syst. p. 165-176.

Weiss, C.M. 1964. Organic pesticides and water pollution. Public Works. 95(12): 84-87.

WHO (World Health Organization). 1976. 1975 Evaluations of Some Pesticide Residues in Food. WHO Pestic. Residue Ser. No. 5, Geneva. p. 242-255.

Wicker, G.W., W.A. Williams and F.E. Guthrie. 1979. Exposure of field workers to organophosphorus insecticides: Sweet corn and peaches. Arch. Environ. Contam. Toxicol. 8(2): 175-182.

Willems, J., R. Braeckman and F. Belpaire. 1980a. Fate of methyl parathion and parathion in the dog. Toxicol. Lett. 5(Sp 1): 34

Willems, J., R. Braeckman and F. Belpaire. 1980b. In vitro extraction of methyl parathion by the liver. Toxicol. Lett. 5(Sp 1): 140.

Williams, M.W., H.N. Fuyat and O.G. Fitzhugh. 1959. The subacute toxicity of four organic phosphates to dogs. Toxicology. 1: 1-7. (Cited in IARC, 1983)

Wills, J.H. 1972. The measurement and significance of changes in the cholinesterase activities of erythrocytes and plasma in man and animals. CRC Critical Reviews in Toxicol. March 1972: 153-202.

Worthing, C.R. and S.B. Walker, Ed. 1983. Pesticide Manual, 7th ed. British Crop Protection Council. p. 420.

Yamamoto, T., T. Egashira, T. Yoshida and Y. Kuroiwa. 1982. Comparison of the effect of an equimolar and low dose of fenitrothion and methylparathion on their own metabolism in rat liver. J. Toxicol. Sci. 7(1): 35-41.

Yamamoto, T., T. Egashira, T. Yoshida, and Y. Kuroiwa. 1983. Comparative metabolism of fenitrothion and methyl parathion in male rats. Acta Pharmacol. Toxicol. 53(2): 96-102.

Zlateva, M. and M. Gurdevski. 1978. Compensatory lung reactions in chronic vofatox poisoning. Med.-Biol. Probl. 6: 132-140. (Bul.) [CA 91(11)84627z]

Zlateva, M. and E. Maleva. 1978. Late morphologic changes in the myocardium of experimental animals after chronic Wofatox poisoning. Eksp. Med. Morfol. 17(2): 99-103. (Bul.) [CA 89(25)211020v]

Zlateva, M. and E. Softova. 1977. Enzyme changes in kidney tissue of experimental animals exposed to chronic poisoning with the organophosphorus preparation vofatox. Nats. Nauchna Ses. Khim. Med. Profil. 2: 351-357. (Bul.) [CA 89(3)18021e]

## APPENDIX

## LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in April and December, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. 94 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. 2879-3816 p.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. 3817-5112 p.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1983. Carcinogenesis Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1983. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call In Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1983. CHIB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (United States International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982. Washington, DC. USITC Publ. 1422.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. Pesticide Manual, 7th ed. British Crop Protection Council. 695 p.